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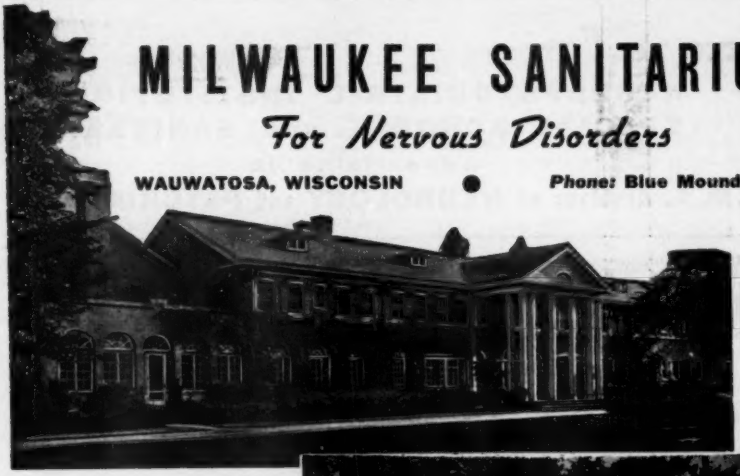

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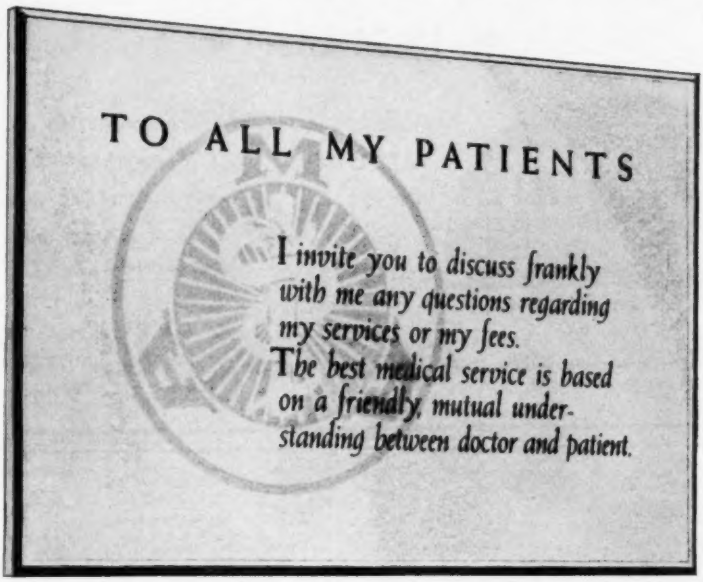
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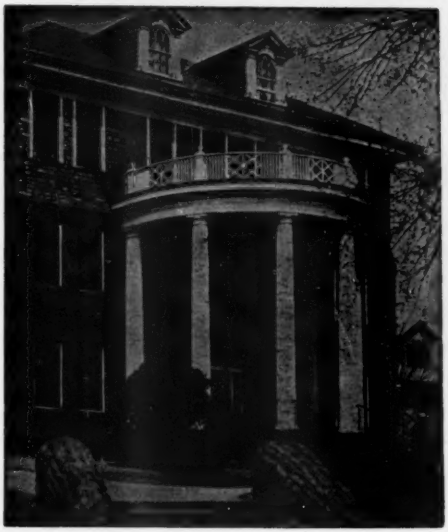

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SUBCORTICAL CONNECTIONS OF THE TEMPORAL POLE IN RELATION TO TEMPORAL LOBE SEIZURES

C. AJMONE MARSAN, M.D.*
AND
J. STOLL Jr., M.D.‡
MONTREAL, CANADA

INTEREST in the subcortical connections of the temporal lobe has increased in recent years, owing to the frequency with which this area becomes the focus of epileptic discharge.

The clinical picture of the form of epilepsy arising from the anterior temporal region has been well known since its original description by Hughlings Jackson [1] in 1871, and its psychical, visceral, motor, and special sensory manifestations do not need a detailed description here.

Recent emphasis upon temporal lobe seizures has been due chiefly to the work of Jasper [2]; Jasper and Kershman [3]; Gibbs, Gibbs, and Fuster [4]; MacLean [5]; Penfield and Flanigin [6]; Bailey and Gibbs [7]; Jasper, Pertuiset, and Flanigin,[8] and Green, Duisberg, and McGrath.[9] The bilaterally synchronous, nonlocalized electro-

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

* Rockefeller Fellow; on leave from the Clinic for Nervous and Mental Diseases, University of Torino, Torino, Italy.

‡ Aided by a fellowship from the National Foundation for Infantile Paralysis, Inc.

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encephalographic abnormalities, which were first described by Gibbs, Gibbs, and Lennox [10] in 1938 as diagnostic of "psychomotor epilepsy," have been more clearly defined in the later studies mentioned above and have been shown to arise in the temporal region, and chiefly in its anterior portion. This contribution from the study of cortical electrical activity and the confirmation by surgical exploration and stimulation of the temporal cortex in man by Penfield and Erickson [11] and Penfield and Rasmussen [12] have shown that so-called psychomotor epilepsy is one form of temporal lobe seizure, perhaps better designated as "epileptic automatism."

In a recent paper presenting the electroencephalographic and electrocorticographic findings of 91 patients with verified temporal lobe seizures, as well as the results of surgical therapy, Jasper, Pertuiset, and Flanigin [8] have shown that, while in 58% of these cases the focus was clearly localized, from the electroencephalographic point of view, to one temporal lobe, bilateral abnormalities, either synchronous or shifting from one side to the other, were present in 42%. They stated that the results of unilateral temporal-lobe excisions, especially when extensive, are better in cases presenting a clearly unilateral electroencephalographic focus. It was found, furthermore, that a small percentage of patients with unilateral excision of the temporal lobe still presented a partial or total recurrence of their habitual seizures, although the removal had been considered, both by electroencephalographic and by pathological criteria, a complete one.

These failures can be explained either by the coexistence of an epileptogenic focus in the opposite temporal lobe (as suggested by MacLean and Arellano [13] and Bailey and Gibbs [7]), or by potentially epileptogenic tissue left in place because it was apparently normal and "nonactive" at the time of operation. However, there remains the possibility that, at least in some cases, the discharges originate in a subcortical structure and project to one or both temporal lobes.

The purpose of the present study is to obtain evidence, even if indirect, for the last hypothesis by studying the subcortical connections of the anterior temporal region, and to shed light on the mechanism by which a discharge in the anterior portion of the temporal lobe is able to give rise to the complex psychical and behavioral disturbances that occur from activation of this region by electrical stimulation or by epileptic discharge. This problem was first undertaken in the cat (Ajmone Marsan, Stoll, and Jasper [14]; and Stoll, Ajmone Marsan, and Jasper,[15] but, because of the poorly developed and ill-defined temporal lobe in this animal, the results obtained, though interesting, can be applied to man only with reservations.

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For this reason, monkeys were used in the present study in order to obtain information more directly applicable to the problem of temporal lobe seizures in man.

METHOD

Experiments were carried out in 18 monkeys, the results for 13 being considered satisfactory. All the studies were done with the animal under pentobarbital anesthesia (0.5 cc. per kilogram being injected intravenously), save one, which was a *cerveau isolé* preparation; i. e., the animal was unanesthetized. Subcortical electrodes for stimulation and recording were inserted by means of a stereotaxic apparatus, and the placements were later checked histologically, the prussian blue reaction being employed for marking the critical areas. Details of operation, stimulation, and recording have been presented in a previous paper.[15]

The methods used included (1) strychnine neuronography; (2) mapping of evoked responses following single electrical stimuli; (3) transmission of electrically induced after-discharges.

Electrical stimulation was carried out in both subcortical areas and on the temporal cortical surface, while strychnine was applied to the temporal cortex and only in a few instances in deeply located regions.

These three physiological methods are mutually complementary in that each provides a different sort of information concerning the connection. Single-pulse stimuli do not reveal the direction of normal conduction of a pathway but enable one to determine the latency, which gives a clue as to how direct the pathway may be. Strychnine neuronography reveals the direction of normal conduction, and the "strychnine spikes" obtained after local application of the drug may be compared with the localized spike discharges, which are the commonest interseizure electroencephalographic findings in the region of an epileptogenic lesion in man. The after-discharge occurring after repetitive electrical stimulation consists of a massive discharge in the area stimulated which electrographically resembles an epileptic seizure discharge and has been shown (Moruzzi[16]; Erickson[17]) to spread along neuronal pathways.

The precision and reliability of the methods employed depend upon the careful control of the various stimuli and upon the method of recording. Cortical areas surrounding the point of application of strychnine were checked for spread of strychnine spikes. The parameters of stimulation for setting up an electrical after-discharge were adjusted to produce an activation only of the point stimulated, and spread was monitored by recording electrodes in adjacent structures. Results obtained with stimulations which were not confined to the restricted area under study were discarded. A row of four steel needle electrodes with an interelectrode distance of 1 mm. was used in subcortical structures. Bipolar recording was employed, since it seemed to give a more precise localization. An example of just how precisely one can localize an evoked electrical response with these methods may be seen in Figure 6. The response shown was recorded from the tip of the temporal lobe after stimulation of the fornix at the spot marked by the arrow only, and no response was obtained by stimulating 1 mm. above or below this point.

RESULTS

The subcortical areas surveyed for both recording and stimulation are limited by the following Horsley-Clarke coordinates: frontal plane, from +2 to +20; lateral plane, from 0 to 9; horizontal plane, from +12 to —4. These coordinates include within their limits the thalamus, the hypothalamus, parts of the surrounding structures, and the basal telencephalic region, from about 2 mm. behind the posterior commissure to about 2 mm. in front of the anterior commissure. Owing to lack of uniformity in size of the monkeys employed in our experiments (from 2 to 8 kg.), the relation of the structures to the Horsley-Clarke coordinates was rather variable.

16. Moruzzi, G.: Contribution à l'électrophysiologie du cortex moteur: facilitation, after-discharge et épilépsie corticales, Arch. internat. physiol. **49**:33-100, 1939.

17. Erickson, T. C.: Spread of Epileptic Discharge: Experimental Study of After-Discharge Induced by Electrical Stimulation of Cerebral Cortex, Arch. Neurol. & Psychiat. **43**:429-462 (March) 1940.

The cortical-stimulating and recording electrodes were placed constantly on the tip of the temporal lobe (Brodmann area 38, area TG of von Bonin and Bailey) bilaterally, an area which is well recognized as the homologue of the anterior temporal pole of man. Other cortical electrodes were at times placed on the uncus, frontal orbital surface, insula, and posterior temporal cortex. These leads were used, as mentioned, to check spread of stimulation and of responses, and some observations were made on these cortical areas as well.

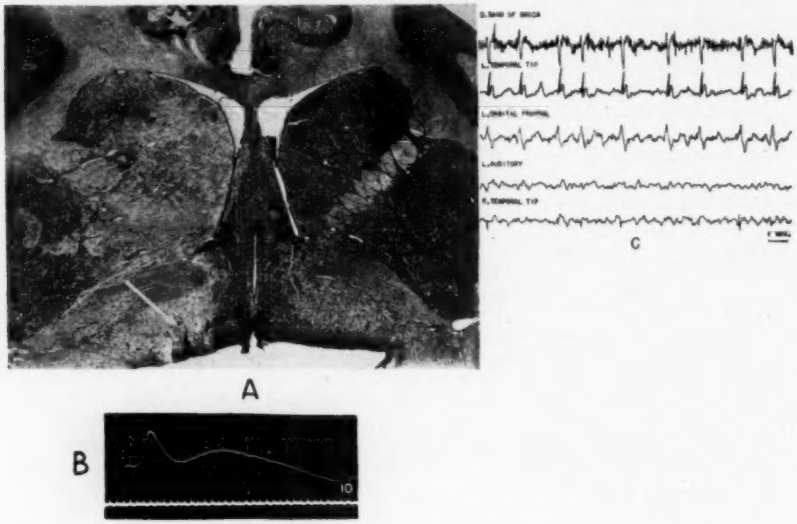

Fig. 1.—Connections between septal areas and temporal tip.

A, arrow pointing to location of tip of electrodes used for stimulation (record *B*) and for recording (record *C*).

B, long-latency evoked response in temporal tip following single-pulse stimulation of septal areas, as shown in *A*. Time: 10 msec.

C, strychnine neuronography. Strychnine spikes evoked in area of diagonal band of Broca (shown by arrow in *A*) by application of drug to left temporal tip. Note slight transmission to the opposite temporal pole.

D (different experiment, same placement of stimulating electrodes), after-discharge set up in homolateral temporal tip and frontal orbital surface after repetitive stimulation of septal regions.

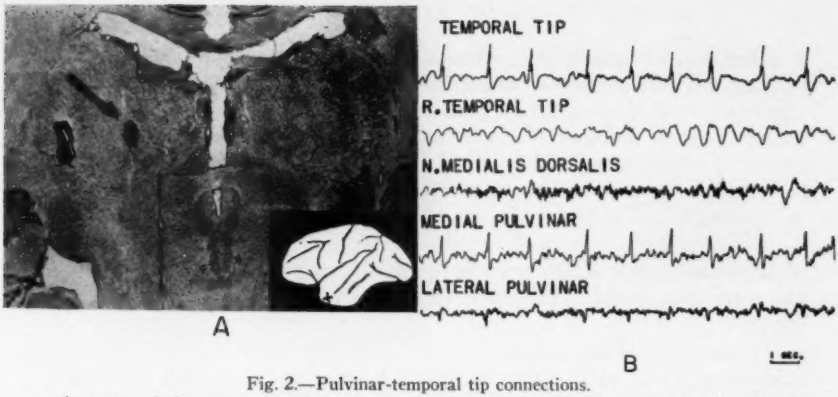

Fig. 2.—Pulvinar-temporal tip connections.

A, arrow pointing to location of tip of recording electrode. The cross marks site of application of strychnine.

B, strychnine neuronography. Spikes evoked in medial portion of pulvinar and, in less pronounced degree, also in lateral portion by application of drug to left temporal pole. Note absence of firing from mesial pair of recording electrodes (nucleus medialis dorsalis).

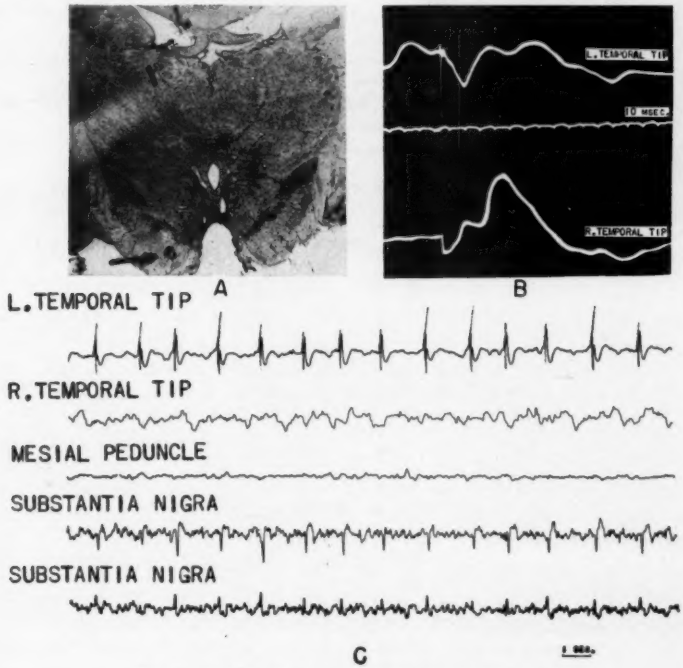

Fig. 3.—Substantia nigra-temporal tip connections.

A, arrow pointing to placement of tip of electrode which was used for stimulating in record *B* and for recording in record *C*.

B, responses evoked in both temporal poles by single-pulse stimulation of left substantia nigra.

C, strychnine neuronography. Spikes evoked in substantia nigra by application of drug to left temporal tip. Note absence of firing in mesial pair of recording electrodes (cerebral peduncle).

Strychnine Neuronography.—The application of strychnine to the tip of the temporal lobe produced spikes which fired into the following subcortical structures: septal area and region of the diagonal band of Broca (Fig. 1); fornix; pulvinar-nucleus lateralis posterior thalamic complex (Fig. 2); nucleus reuniens of the thalamus; substantia nigra (Fig. 3); globus pallidus. Transmitted spikes were also recorded in the anterior portion of the internal capsule, the cerebral peduncle, and the anterior commissure.

Several attempts were made to induce spikes after local application of a crystal of strychnine through a hollow needle in the septal areas, without success, although they were easily evoked in the same areas in the cat (Stoll, Ajmone Marsan, and Jasper [15]).

Conduction of Electrical After-Discharge.—When, after repetitive stimulation (sine wave; 25 to 60 cps; 2 to 6 volts; 3-to-6 seconds' duration), a local after-discharge was set up in the temporal pole, synchronous self-sustained activity was recorded in the septal areas, nucleus lateralis posterior of the thalamus; nucleus

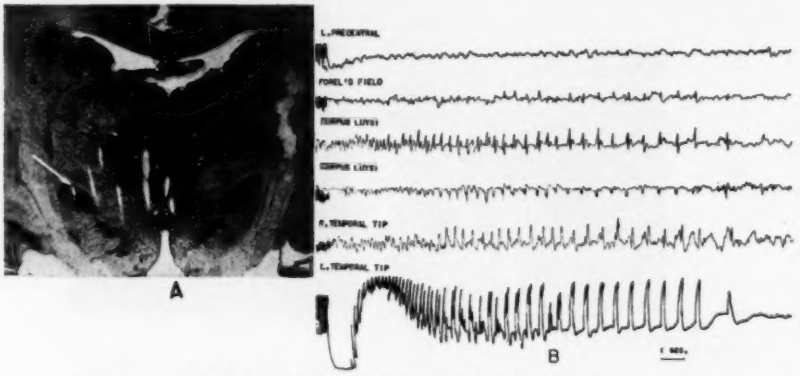

Fig. 4.—Corpus Luysi-temporal tip connections.

A, arrow pointing to location of tip of recording electrode.

B, Local after-discharge evoked by repetitive stimulation of left temporal pole, firing into the corpus Luysi. Note transmission of after-discharge to opposite temporal pole.

reuniens of the thalamus, and corpus Luysi (Fig. 4). The same activity was recorded in the cerebral peduncle and in the anterior portion of the internal capsule.

An after-discharge was recorded in the tip of the temporal lobe after repetitive stimulation of the following subcortical structures: septal areas (Fig. 1), nucleus lateralis dorsalis of the thalamus, nucleus reuniens of the thalamus, substantia nigra, and caudate nucleus.

Repetitive stimulation of the septal areas gave rise occasionally to bilateral discharge in the temporal tips. When the nucleus lateralis dorsalis of the thalamus was similarly stimulated, the after-discharge recorded was not so strictly localized in the temporal tip but appeared also, and at times only, in the uncus (Fig. 5).

The parameters of stimulation required to set up an after-discharge in subcortical structures differed slightly from those required to produce a cortical after-discharge; higher voltage and frequency seemed more effective (sine wave; 100

cps; 6 to 10 volts). As stated in a previous paper,[15] however, the parameters of stimulation necessary to set up an after-discharge, both in the cortex and in the sub-

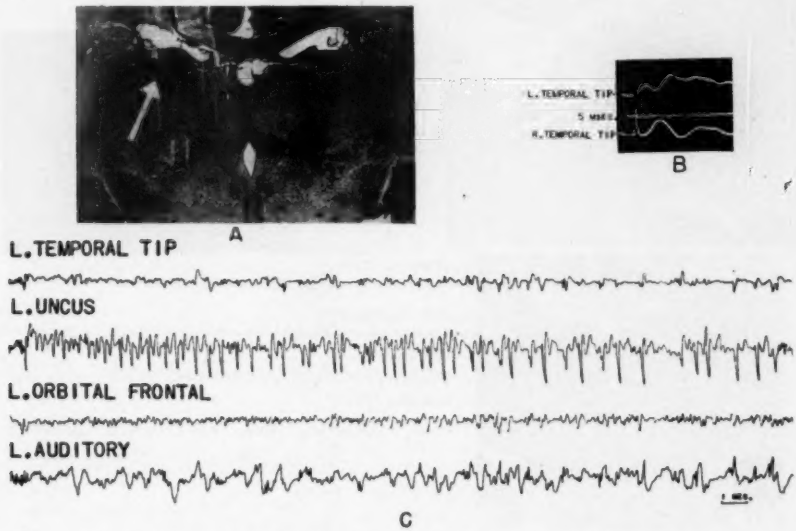

Fig. 5.—Connections of nucleus lateralis dorsalis and temporal tip and uncus.
A, arrow pointing to placement of stimulating electrode in thalamus.
B, responses evoked in both temporal tips by single-pulse stimulation of nucleus lateralis dorsalis of thalamus.
C, after-discharge set up in uncus after repetitive stimulation of nucleus dorsalis of he thalamus.

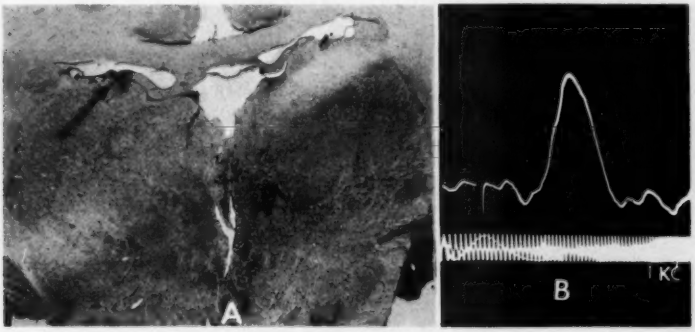

Fig. 6.—Fornix-temporal tip connections.
A, arrow showing placement of tip of stimulating electrode.
B, response evoked in homolateral temporal tip by single-pulse stimulation of fornix.

cortical structures, were found to vary rather widely, depending upon the condition of the animal and the level of anesthesia.

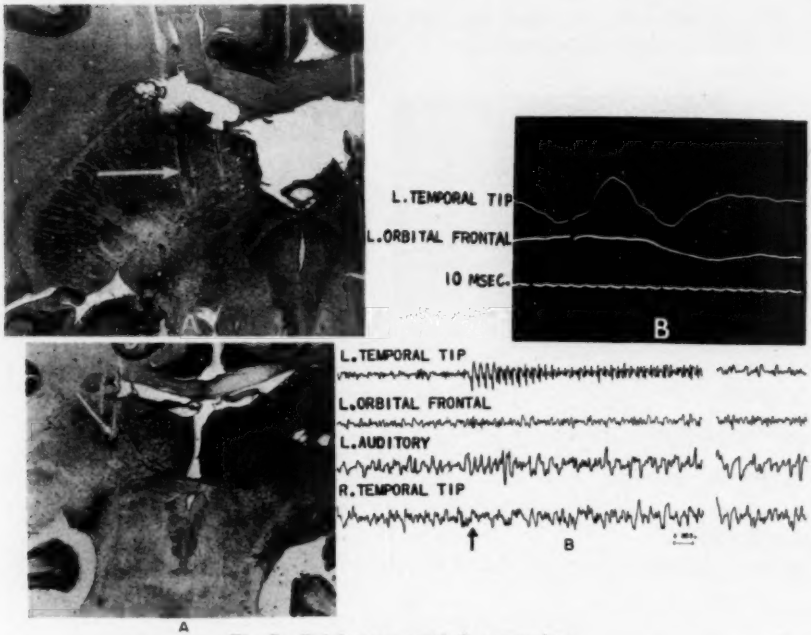

Fig. 7.—Pulvinar-temporal tip connections.

Above: *B*, response evoked in homolateral temporal tip by single-pulse stimulation of pulvinar in area marked by arrow (*A*). Note absence of response in adjacent frontal orbital surface.

Below (different experiment): *B*, responses evoked in homolateral temporal tip by brief stimuli repeated at 3 cps in pulvinar (see arrow in *A*).

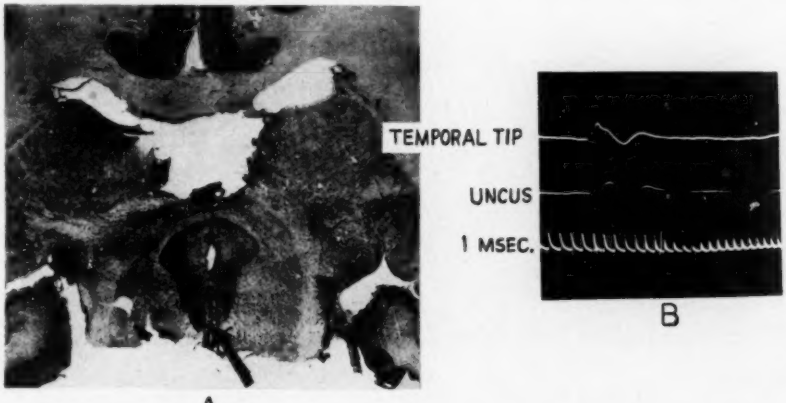

Fig. 8.—Connections of periaqueductal gray substance and temporal tip and uncus.

A, placement of tip stimulating electrode as shown by the arrow. *B*, brief-latency responses evoked in tempoarl tip and uncus by single-pulse stimulation of the periaqueductal gray substance.

Mapping of Evoked Potentials.—Evoked potentials were recorded in the tip of the temporal lobe after stimulation with single pulses (square wave; duration, 0.5 to 1.0 msec.; average voltage, 6 to 10) of the following subcortical structures: septal areas and region of the diagonal band of Broca (Fig. 1); fornix (Fig. 6); hypothalamus; nucleus lateralis dorsalis, pulvinar, and nucleus lateralis posterior of the thalamus (Figs. 5 and 7); centrum medianum, and nucleus reuniens of

Latencies of Responses in the Temporal Tip Obtained on Stimulation of Various Subcortical Structures by Three Electrophysiological Methods

Subcortical Structure	Experiment	Single-Pulse Stimulation	After-Discharge	Strychnine	Latency (Msec.) No. Determinations	Latency (Msec.) Range	Latency (Msec.) Mean
N. lateralis posterior and pulvinar...	A-57	..	..	+	..	.....	....
	A-46	+	+	..	..	.....	....
	A-39	..	..	+	..	.....	....
	A-47	+	..	..	25	12-20	14.5
	A-48	..	..	+	..	.....	....
	A-49	+	..	..	..	.....	....
	A-51	+	..	..	..	.....	....
	A-56	..	..	+	..	.....	....
N. lateralis dorsalis.....	A-46	+	..	..	..	.....	....
	A-48	+	..	..	18	4-7.5	6.2
	A-49	+	..	..	..	.....	....
	A-51	..	+	..	..	.....	....
Septal area.....	A-38	+	+	..	..	.....	....
	A-39	..	+	+	8	17.5-30	24.2
	A-54	..	..	+	..	.....	....
Diagonal band of Broca.....	A-48	+	..	..	..	.....	....
	A-54	..	..	+	11	18-30	24.9
	A-55	..	..	+	..	.....	....
Caudate nucleus.....	A-51	..	+	..	..	.....	....
Globus pallidus.....	A-56	..	..	+	..	.....	.. .
Red nucleus.....	A-49	+	..	..	3	2	2
Substantia nigra.....	A-49	+	+	..	..	.....	....
	A-56	..	..	+	9	5-8	7.1
	A-57	..	..	+	..	.....	....
Corpus Luysi.....	A-48	+	..	..	..	.....	....
	A-55	..	+	..	4	25-46	40.2
Hypothalamus	A-44	+	..	..	..	.....	....
	A-49	+	..	..	10	2-2.6	2.5
	A-55	..	+	..	..	.....	....
Centrum medianum.....	A-44	+	..	..	..	.....	25
N. reuniens.....	A-48	+	..	..	7	12-20	15.8
	A-39	..	+	+	..	.....	....
Central gray substance.....	A-49	+	..	..	22	1-2	1.5

the thalamus; substantia nigra (Fig. 3), corpus Luysi, and red nucleus; periaqueductal central gray substance (Fig. 8), and anterior commissure.

Evoked potentials were recorded in both temporal poles when the anterior commissure, the substantia nigra, and the nucleus reuniens and nucleus lateralis posterior-pulvinar complex of the thalamus were stimulated.

The average latencies of the responses obtained from the various structures mentioned are included in the summarizing table and diagram (Table and Fig. 9). The figures obtained point clearly to the existence of a number of synapses in the pathways connecting the temporal pole with some of the subcortical structures mentioned above, namely, the septal areas, corpus Luysi, nucleus reuniens and

centrum medianum of the thalamus. On the other hand, other structures, such as the hypothalamus, the nucleus lateralis dorsalis of the thalamus, the red nucleus, and the periaqueductal central gray substance have latencies which would be compatible with direct pathways to the temporal tip.

The mean value of the latencies found for the responses in the temporal tip when the nucleus lateralis posterior-pulvinar complex of the thalamus or the substantia nigra were stimulated might be consistent with either a multisynaptic pathway or small-caliber, slowly conducting fiber tracts. The second possibility

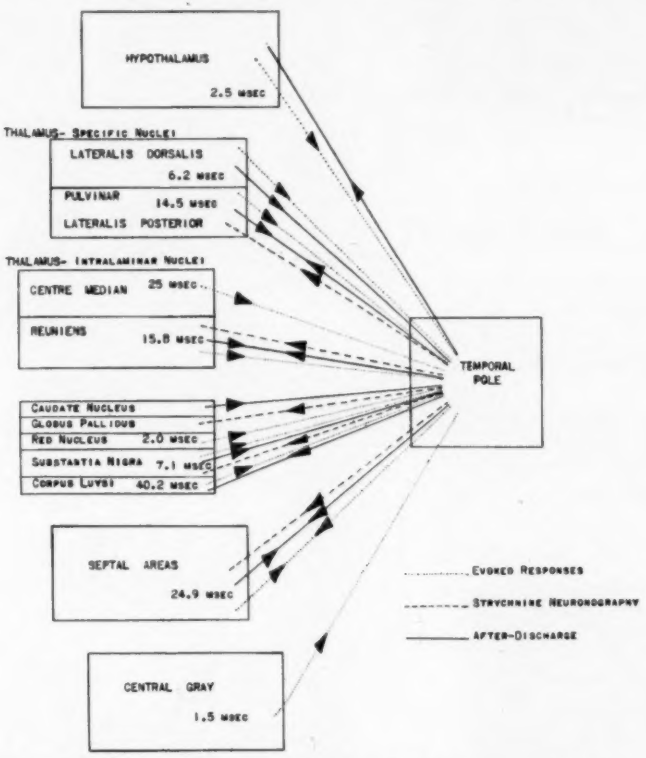

Fig. 9.—Diagram summarizing subcortical connections of temporal pole in the monkey found by means of three electrophysiological methods. Figures correspond to mean latencies observed when responses to brief single-pulse stimulation were evoked (Table). Arrows indicate direction of conduction found with the different methods.

must be considered when one takes into account the long latencies observed in well-established thalamocortical pathways, such as the nucleus medialis dorsalis-frontal lobe connections, in which case the latency of the evoked response is more than 7 msec., as shown in Figure 10.

The accompanying table permits an objective evaluation of our findings. It can be seen, in fact, that some connections were confirmed in a relatively large number

of experiments and still others were occasionally found, noted in a single experiment and demonstrated by a single method. We feel that, whereas the more constant findings are significant and point to the existence of connections with the anterior part of the temporal lobe, the less constant results obviously require further confirmation before they can be fully accepted. Thus, in evaluating the significance of the functional and clinical implications of the individual connections, to be discussed below, one must take into account that some are presented with this reservation.

Although the structures adjacent to the tip of the temporal lobe were not systematically surveyed for subcortical connections, occasional observations were made which we feel are worth mentioning here.

Evoked responses in the uncus were recorded after single-pulse stimulation in the hypothalamus, the nucleus lateralis dorsalis, the nucleus medialis dorsalis, the nucleus lateralis posterior-pulvinar complex of the thalamus, the periaqueductal

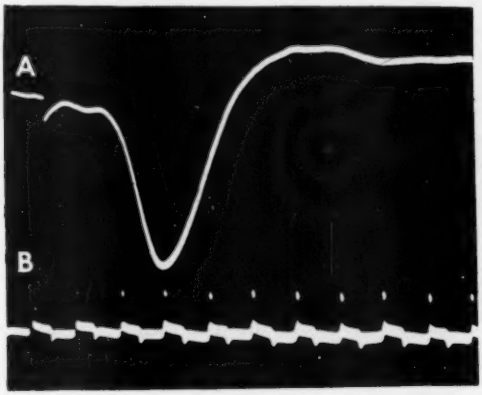

Fig. 10.—Long-latency response observed in a direct thalamocortical pathway.
A, response evoked in the frontal pole after single-pulse stimulation of the nucleus medialis dorsalis of the thalamus. *B*, time signal record: 5 msec.

gray substance (Fig. 8), the red nucleus, and the brachium conjunctivum. After-discharge in the uncus was recorded after repetitive stimulation of the caudate nucleus, the substantia nigra, and the nucleus medialis dorsalis and nucleus lateralis dorsalis of the thalamus (Fig. 5).

On the orbital surface of the frontal lobe evoked responses were recorded (in one experiment) after single-pulse stimulation of the nucleus medialis dorsalis and nucleus lateralis posterior-pulvinar complex of the thalamus and the corpus Luysi. After-discharge was recorded in the same cortical area after repetitive stimulation of the septal regions (Fig. 1).

Observations made on corticocortical connections include the transmission of both strychnine spikes and after-discharge from the temporal tip to the adjacent uncus and frontal orbital surface. Connections between the two temporal tips were shown by all three methods. The latency of the evoked response in one tip on

square-wave, single-pulse stimulation of the opposite temporal tip varied from 13 to 25 msec. Strychnine spikes were not as readily transmitted across to the opposite temporal tip as was the after-discharge (Figs. 1 and 4).

COMMENT

The results of the present work on monkeys may be compared with those in similar experiments carried out on cats.[15]

On the whole, the subcortical connections of the tip of the temporal lobe seem to correspond fairly well in the two species. The nucleus lateralis posterior-pulvinar complex of the thalamus, the centromedian nucleus of the thalamus, the septal area-fornix system, the hypothalamus, and parts of the basal ganglion system were found to be functionally connected with the temporal pole in both series of experiments. Differences in the results, however, were found in the two species; some of these noncorresponding points seem to us to be of significance. The connection between the anterior thalamic nuclei and the tip of the temporal lobe established in the cat, for instance, was not found in the monkey. On the other hand, the connection with the nucleus lateralis dorsalis of the thalamus, rather constantly found in the monkey, was not shown in the cat.

The connection with the septal area-fornix system, though common to both species, seemed to be more easily and frequently demonstrated in cats; the connections with the nucleus lateralis posterior-pulvinar complex of the thalamus were more easily demonstrated in monkeys.

These differences suggest that in the more primitive species the temporal pole represents transitional cortex, functionally related both to the archipallium and to the neopallium. As the phylogenetic scale is ascended, this region seems to become physiologically more closely related to the neopallium, although connections with the more primitive type of cortex still exist.

The number of connections found and their apparent heterogenicity provide a possible explanation for the complexity of the phenomena which accompany epileptic activation of the anterior temporal region and form a basis for speculation concerning the pathogenesis of these phenomena. The connections delineated are schematically represented in Figure 11 and may be divided into five groups, according to their possible functional significance.

Nucleus Lateralis Posterior-Pulvinar Complex of the Thalamus.—One of the most constant findings was the connection with the nucleus lateralis posterior-pulvinar complex of the thalamus; it was confirmed in both cat and monkey. Anatomical methods had failed to reveal any connections between the anterior temporal region and the thalamus until recently, when Li[18] (1950), using the Marchi method, and Chow[19] (1950), with degeneration studies following more or less local ablations in the anterior temporal region of the monkey, showed connections with the pulvinar. Our results indicate a rather scattered projection of the temporal tip throughout the pulvinar-nucleus lateralis posterior complex. This diffuse projection of a relatively small cortical area to and from a comparatively

18. Li, C. L.: Anatomical Studies of Temporal Polar Cortex in Cat and Monkey, Thesis, McGill University, 1950.

19. Chow, K. L.: A Retrograde Cell Degeneration Study of the Cortical Projection Field of the Pulvinar in the Monkey, J. Comp. Neurol. **93**:313-340, 1950.

large thalamic structure may possibly explain the meager information provided by traditional anatomical methods. The scarcity of positive results in degeneration studies following ablations of the temporal lobe may also find an explanation in the fact that the projecting thalamocortical fibers very likely have widely distributed collaterals which protect the thalamic cells of origin from degeneration.

This anterior temporal-pulvinar relationship would seem to place this cortical area in closer connection with the more important association cortex of the posterior temporal and parietal regions and may provide an anatomical basis for the complex psychical manifestations that frequently occur in the temporal lobe seizures. The

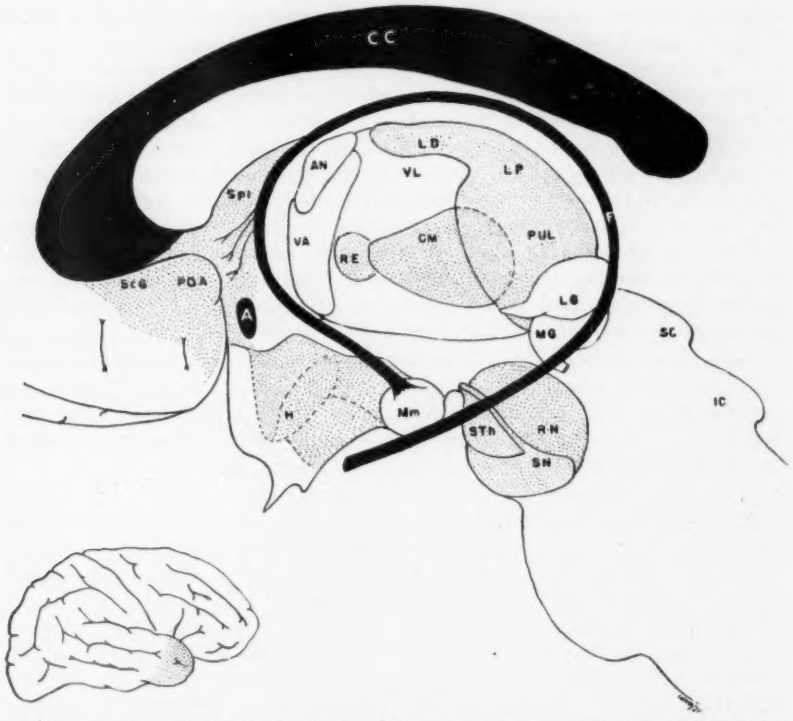

Fig. 11.—Schematic drawing showing in outline (dotted areas) principal subcortical structures found to be functionally related to the temporal pole in the monkey.

A indicates anterior commissure; *AN*, anterior nuclei of thalamus; *CC*, corpus callosum; *CM*, centrum medianum of thalamus; *F*, fornix; *H*, hypothalamus; *IC*, inferior colliculus; *LD*, nucleus lateralis dorsalis of thalamus; *MG*, medial geniculate body; *Mm*, mamillary body; *POA*, paraolfactory area; *Pul*, pulvinar; *RE*, nucleus reuniens of thalamus; *RN*, red nucleus; *SC*, superior colliculus; *SCG*, subcallosal gyrus; *SN*, substantia nigra; *SPt*, septal areas; *STh*, corpus Luysi; *VA*, nucleus ventralis anterior of thalamus; *VL*, nucleus ventralis lateralis of thalamus.

nucleus lateralis dorsalis of the thalamus, for which connections were also found with the temporal tip, may reasonably be included in the same system. The relatively late development in the phylogenetic scale of these lateral nuclei, along with the association cortex, seems to support this assumption.

The Septal Region.—The connections with the septal region found in the cat experiments were also shown, though not as consistently, in the present work on the monkey. While in the cat the septal nuclei, fairly well developed in this species, seem to represent the principal area connected with the temporal tip, in the monkey the connections seemed to be more diffusely scattered in the basal portions of the septal region, namely, in the anterior olfactory area, the nucleus accumbens, and the diagonal band of Broca. Evidence obtained in the experiments on cats suggested that the fornix may provide a pathway for conduction between the septal area and the temporal tip. It seems reasonable, therefore, to assume that some fibers of this important tract have a similar function in monkeys, and the potentials evoked in the temporal tip of these animals after electrical stimulation of the fornix (Fig. 6) support this assumption.

The homologue in man of the septal region described in the monkey is not so clearly defined, but is probably represented by the gray matter at the base of the septum pellucidum, including the parolfactory area and the subcallosal gyrus (area 25 of Brodmann), as well as the septum pellucidum itself. Thus, the close relation of the tip of the temporal lobe, the uncus, the hippocampus, and the parolfactory area seems not only one of topographical contiguity but also a functional one via the fornix-hippocampus system. The uncinate fits, dreamy states, and emotional and olfactory components which are frequently associated with temporal lobe seizures may find their anatomical substrate in this system. Further evidence suggesting the possible significance of this region will be presented later in the discussion of the electroencephalographic aspects of the problem.

The Hypothalamus.—The connections found between the temporal pole and the hypothalamus were scattered throughout the extent of this region, and it was not possible to localize these connections to any specific hypothalamic nuclei. This region may be the one through which impulses set up by activation of the temporal tip are capable of giving rise to autonomic and visceral phenomena.

The Basal Ganglion Structures.—We include in this group the substantia nigra, corpus Luysi, globus pallidus, caudate nucleus, and red nucleus. They did not yield constant responses as individual components, but when they were considered as a system a fair number of responses were found. This is in agreement with our findings in cats, and we feel justified, therefore, in suggesting the existence of connections between this system and the temporal pole. The motor inhibitory phenomena produced by stimulation of this region (Kaada, Pribram and Epstein [20]; Kaada [21]), as well as the tonic postural and other motor manifestations of its epileptic activation, may be explained by these connections. The automatic behavior ("psychomotor" manifestations) during these seizures is possibly best explained [12] as an arrest of certain psychical functions, as suggested originally by Hughlings Jackson.

Thalamic Reticular System.—The demonstration of the existence of connections with thalamic nuclei (centrum medianum and nucleus reuniens) recognized

20. Kaada, B. R.; Pribram, K. H., and Epstein, J. A.: Respiratory and Vascular Responses in Monkeys from Temporal Pole, Insula, Orbital Surface and Cingulate Gyrus, J. Neurophysiol. **12**:347-356, 1949.

21. Kaada, B. R.: Somato-Motor, Autonomic and Electrocorticographic Responses to Electrical Stimulation of "Rhinencephalic" and Other Forebrain Structures in Primates, Cat and Dog, Acta physiol. scandinav. Supp. 83, p. 1, 1951, to be published.

(Jasper [22]) as part of the thalamic reticular system suggests that the anatomical substrate for the participation of the anterior temporal region in the recruiting type of response demonstrated in the cat is present also in the monkey. The functional significance of these connections as related to the problem of temporal lobe seizures is not clear, although it may have some bearing on the alterations in consciousness which occur. In relation to the question of impairment of consciousness, the apparently direct connection between the periaqueductal gray substance and the temporal tip and uncus may be mentioned here. This connection was a single finding, noted in an experiment in which the subcortical electrodes were placed more posteriorly than usual (Fig. 8), but it seems to be of interest in view of the common clinical experience that lesions in this region are likely to produce unconsciousness. This functional connection between the central gray substance and the uncus, moreover, may be related to the recent findings of Liberson, Scoville, and Dunsmore,[23] who observed constant alterations of consciousness after stimulation of the uncus in man.

The points found throughout the white matter of the internal capsule and cerebral peduncle were probably in the fibers of the well-known temporopontile tract. The function of this pathway is not clearly established, but its probable relation to the extrapyramidal system and to the reticular formation of the pons suggests another basis for the pathogenesis of the tonic motor phenomena which accompany activation of the temporal lobe by epileptic discharge.

A detailed study of the corticocortical connections was not carried out, but the few observations made in the course of the experiments confirm the functional relation of the tip of the temporal lobe to the uncus and orbital surface of the frontal lobe.

Correlation with Clinical Electroencephalographic Findings.—The results presented and already discussed, chiefly in relation to the clinical manifestations of temporal lobe seizures, appear to be of interest also in relation to the electroencephalographic picture of these disorders, which, as stated in the introduction, often presents problems in interpretation. This is especially true in those cases which are characterized by bilateral disturbances, either synchronous or asynchronous.

When the bilateral abnormalities are obviously the result of transmission from a focus located in one temporal lobe to the other side, they do not present a real diagnostic problem. These cases, classified as Group II by Jasper, Pertuiset, and Flanigin,[8] have been shown by the same authors usually to be associated with lesions in the temporal pole and uncus. Experimentally, we have been able to confirm this observation by showing the existence of connections between the two tips (as have Sugar, French, and Chusid [24]). Tip-to-tip cross firing was, however, easier to elicit with a massive volley of impulses (after-discharge) than by strychnine neuronography. This finding could be explained by fairly discrete point-to-

22. Jasper, H. H.: Diffuse Projection Systems: The Integrative Action of the Thalamic Reticular System, Electroencephalog. & Clin. Neurophysiol. **1**:405-419, 1949.

23. Liberson, W. T.; Scoville, W. B., and Dunsmore, R. H.: Stimulation Studies of the Prefrontal Lobe and Uncus in Man, Electroencephalog. & Clin. Neurophysiol. **3**:1-8, 1951.

24. Sugar, O.; French, J. D., and Chusid, J. G.: Cortico-Cortical Connections of the Superior Surface of the Temporal Operculum in Monkey (Macaca Mulatta), J. Neurophysiol. **11**:175-184, 1948.

point commissural connections or by the fact that a volley of discharges may facilitate or open up synaptic barriers. In fact, the presence of synaptic relays in this pathway is strongly suggested by the long latency (from 13 to 25 msec.) observed when responses were evoked in one temporal pole after single-pulse stimulation of the other, or in both poles after stimulation of the anterior commissure, which is probably one of the pathways involved in this connection. However, it appears from some of our results that the anterior commissure, as well as the anterior portion of the corpus callosum, may not be the only pathway between the two tips. The demonstrated functional connection between the temporal pole and the fornix suggests that the commissure of the fornix, or psalterium, may provide another means by which activity in one temporal pole may be transmitted to the opposite side.

The cases in which the electroencephalographic abnormalities cannot be lateralized and appear with equal amplitude on the two sides, being either synchronous or shifting from one side to the other (Groups III and IV of Jasper, Pertuiset, and Flanigin [8]) are frequently encountered in routine electroencephalographic examinations and comprise from 25 to 42% according to the figures of Gibbs and associates,[4] Gastaut,[25] and Jasper and associates.[8] For cases of this type, which often present the more intriguing diagnostic problems, there are, as already stated, various theoretically possible interpretations.

One possibility would be that in at least some cases of bilaterally synchronous abnormality one is dealing with a primary unilateral focus with contralateral transmission. The similarity of the amplitude and form observed in the abnormal potentials of the two sides would not favor this interpretation, since experimentally the transmitted phenomena following either strychninization or electrical after-discharge were never identical with the primary phenomena. They showed, instead, a lower amplitude and a longer time course. However, one should consider the hypothetical possibility that in long-standing temporal lobe epilepsy the repeated activation of the opposite, originally normal, side by the primary focus may produce in it functional changes, manifested by an abnormal hypersensitization to cross firing. The last hypothesis is worth further experimental investigation.

Two other possible interpretations of bilaterally synchronous discharges should be considered when one is employing electroencephalographic findings as criteria in the selection of patients with temporal lobe seizures for surgical therapy. One is the existence of bilateral foci in the anterior temporal regions; the other is the possibility that disturbances may not be primarily cortical but may be conducted from a subcortical epileptogenic focus.

The first possibility seems likely in some cases, especially when the electroencephalographic foci appear to shift from one side to the other and when the susceptibility of the anterior temporal areas to injury and to noxious agents is taken into account.

The second hypothesis, which was suggested by Jasper [2] and Jasper and Kershman,[3] was indirectly correlated with pathological-electroencephalographic

25. Gastaut, H.: Le lobe temporal en oto-neuro-ophtalmologie; étude électro-encéphalographique, in Reports of the International Congress of Otology, Neurology, and Ophthalmology, Barcelona, May, 1950, Paris, Gaston Doin & Cie, Chap. 6.

evidence by Walter and Dovey [26] and Lennox and Brody [27] and seems experimentally to be shown possible by the present results. Bilateral temporal tip responses were, in fact, obtained from the septal region, the nucleus lateralis posterior-pulvinar complex of the thalamus, the nucleus reuniens of the thalamus, and the substantia nigra. These responses were always bilaterally synchronous, and no evidence of asynchronous firing was observed.

Any one of these subcortical structures which connect with both temporal tips might be considered as a point on an arc-like pathway going from one tip to the subcortical structure itself and then to the opposite tip. Thus, theoretically, and provided that similar connections exist in man, if any one of the three points on the pathway should become activated by an epileptogenic discharge, the other two points may well become involved, and very likely synchronously, so that a focus in one tip or in any one of the subcortical structures may give rise to bilaterally synchronous temporal discharges.

An attempt was made to obtain clinical support for the hypothesis of the subcortical origin of bilateral temporal discharges by looking for x-ray evidence of midline lesions around the parolfactory area in a series of cases showing symptoms suggestive of "psychomotor" epilepsy and electroencephalographic disturbances localized in one or both temporal lobes. Nine cases were found with pneumographic evidence of a cyst of the septum pellucidum. These few cases are obviously not enough to prove our hypothesis, but they are mentioned in the interest of the suggestion that a pathological study on a large number of cases may prove to be more fruitful.

A possible explanation of the few unsatisfactory results obtained in cases of rather complete excisions of the temporal lobe focus in the patients presenting only unilateral electroencephalographic abnormalities or with slight transmission to the opposite side (Groups I and II of Jasper, Pertuiset, and Flanigin [8]) is afforded by our results. Since after stimulation of almost all the various subcortical structures, responses could be evoked in the homolateral temporal tip, the theoretical possibility exists (as suggested by Meyers and associates [28]) that at least some unilateral electroencephalographic disturbances may be, instead, purely conducted abnormalities from subcortical areas and do not necessarily indicate the existence of a cortical epileptogenic focus.

SUMMARY AND CONCLUSIONS

A better understanding of the subcortical connections of the temporal pole appears to be of primary importance, owing to the fact that this cortical region is frequently the focus of epileptic discharge.

An experimental approach to this problem was undertaken on lightly anesthetized monkeys, employing three electrophysiological methods for mapping connec-

26. Walter, W. G., and Dovey, V. J.: Electro-Encephalography in Cases of Subcortical Tumours, J. Neurol., Neurosurg. & Psychiat. **7**:57-65, 1944.

27. Lennox, M., and Brody, B. E.: Paroxysmal Slow Waves in the Electroencephalograms of Patients with Epilepsy and with Subcortical Lesions, J. Nerv. & Ment. Dis. **104**:237-248, 1946.

28. Meyers, R.; Knott, J. R.; Hayne, R. A., and Sweeney, D. B.: The Surgery of Epilepsy: Limitations of the Concept of the Cortico-Electrographic "Spikes" as an Index of the Epileptogenic Focus, J. Neurosurg. **7**:337-346, 1950.

tions: (*a*) strychnine neuronography, (*b*) conduction of electrically induced after-discharges, and (*c*) evoked potentials.

The subcortical structures found to be functionally connected with the temporal pole may be classified under the following heads: (*a*) pulvinar-nucleus lateralis posterior complex of the thalamus; (*b*) septal area-fornix system; (*c*) hypothalamus; (*d*) basal ganglion system; (*e*) thalamic reticular system (centrum medianum reuniens).

Latency studies of the responses obtained suggest that the pathways involved between the temporal pole and the septal areas, part of the basal ganglion system, and part of the thalamic reticular system are multisynaptic. The pathways between the temporal pole and the hypothalamus, nucleus lateralis dorsalis of the thalamus, and part of the basal ganglion system are probably direct, whereas for the pulvinar-nucleus lateralis posterior complex of the thalamus the latencies may be consistent with either a multisynaptic connection or a slowly conducting, small-caliber direct fiber tract. Projections to and from the temporal pole with the pulvinar-nucleus lateralis posterior complex of the thalamus were diffuse and scattered throughout this thalamic nuclear mass.

The findings obtained in monkeys confirm those reported in a previous series of experiments on cats.

The possible clinical significance of the different subcortical connections of the temporal pole are discussed in relation to the heterogenous manifestations of activation of the temporal lobe by electrical stimulation or by epileptic discharge.

The electroencephalographic pictures commonly observed in cases of focal cerebral seizures with temporal pole localization are reviewed, and emphasis is given to the bilaterally synchronous abnormalities and to their possible pathophysiological substrate.

It is suggested that in at least some cases bilaterally synchronous discharges and unilateral abnormalities recorded in the electroencephalogram of patients with temporal lobe seizures may be of subcortical origin.

We received assistance from Dr. H. H. Jasper in the experiments, as well as in the preparation of the manuscript.

Dr. J. Olszewski assisted in the study of anatomical sections.

ACUTE VASCULAR LESIONS OF THE BRAIN STEM

A Complication of Supratentorial Space-Occupying Lesions

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PONTINE hemorrhage frequently has been noted at necropsy in cases of supratentorial tumor. This has not been an uncommon finding at the Mayo Clinic during the last five years, but prior to 1940 pontine hemorrhage rarely was noted at necropsy in cases of tumor of the brain. This study of vascular lesions of the brain stem was undertaken to aid in the clinical recognition of such lesions in the presence of other intracranial lesions and to investigate the possible mechanisms causing the hemorrhage.

In 1903, Dana [1] reported the results of a study of lesions of the brain stem. He said that pontine hemorrhage was rather rare and that it accounted for 1 to 10% of all intracranial hemorrhages. Attwater,[2] in 1911, in a review of 67 cases of pontine hemorrhage which had been observed at Guy's Hospital in the previous 36 years, found that necropsy disclosed a small secondary pontine hemorrhage and a large primary hemorrhage into the internal capsule in about 30% of the cases. In 12 of the 67 cases the pontine hemorrhage appeared to be the direct result of severe injury of the skull. Greenacre,[3] in 1917, stressed the occurrence of pontine hemorrhage in association with spontaneous intracranial hemorrhage. According to this author, a pontine hemorrhage occurred in conjunction with a hemorrhage into the internal capsule or basal ganglia in 15 of 128 cases of intracranial hemorrhage. She attributed the hemorrhage in the brain stem to the rise in intra-arterial tension secondary to the increase in extracranial blood pressure.

In 1923, Bagley [4] reported three cases in which the clinical course was similar (a sharp rise in temperature to a hyperpyrexic state and elevation of the pulse and respiratory rates). In two of these cases necropsy disclosed multiple hemorrhages in the basal ganglia. An illustration showed hemorrhage in the midline of the mesencephalon in one of these cases.

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1. Dana, C. L.: Acute Bulbar Paralysis Due to Hemorrhage and Softening of the Pons and Medulla, with Reports of Cases and Autopsies, M. Rec. **64**:361-366, 1903.

2. Attwater, H. L.: Pontine Haemorrhages, Guy's Hosp. Rep. **65**:339-389, 1911.

3. Greenacre, P.: Multiple Spontaneous Intracerebral Hemorrhages: A Contribution to the Pathology of Apoplexy, Bull. Johns Hopkins Hosp. **28**:86-88 (Feb.) 1917.

4. Bagley, C., Jr.: Extensive Hemorrhagic Extravasation from the Venous System of Galen, with a Clinical Syndrome, Arch. Surg. **7**:237-257 (Sept.) 1923.

Wilson and Winkelman,[5] in 1925, reported 13 cases of pontine hemorrhage. Multiple hemorrhages were present in most of the cases. In each case an extrapontine lesion was present. These lesions were the result of trauma in five cases, of neoplasm in three cases, and of abscess in one case. These authors found that pontine hemorrhage occurred in 6% of cases of tumor of the brain and in 20% of cases of cranial trauma in which necropsy was performed.

Rosenhagen,[6] in 1932, reported his observations on pontine and tegmental hemorrhage as a complication of cerebral tumor. He said that the hemorrhage was associated with generalized stasis and dilatation of the pontine vessels. In one year Rosenhagen observed microscopic hemorrhages in the brain stem in 10 of 16 cases of cerebral tumor.

Van Gehuchten,[7] in 1937, reported five cases of cerebral glioma and one case of tuberculoma. In these cases tentorial herniation and hemorrhage into the brain stem were associated findings. Sudden death occurred after lumbar puncture in two of these six cases, and it followed ventriculography in two cases. In each of the four cases in which death occurred suddenly, the coma occurred shortly after the diagnostic procedure. Included in this report were the comments of Clovis Vincent, whose experience led him to believe that the removal of the tumor does not necessarily relieve the tentorial herniation, since the cerebral edema remains and thus maintains the herniation.

Jefferson,[8] in 1938, called attention to the clinical manifestations of the tentorial pressure cone, or herniation of the temporal lobe. He found that contralateral pyramidal signs, stiffness of the neck, nuchal pain, anisocoria, and bilateral rigidity occurred when a supratentorial tumor produced herniation of the uncus of the temporal lobe.

Moore and Stern,[9] in 1938, reported vascular lesions in the brain stem and occipital lobe as a complication of tumors of the brain. In 14% of a series of 130 brains in which a tumor or an abscess was found, hemorrhage was present in the upper portion of the brain stem.

None of the cases showed focal symptoms which were suggestive of a pontine or mesencephalic lesion. In those cases in which the clinical picture gave any evidence at all of a lower brain stem hemorrhage, the state of coma did not clear up sufficiently to permit an evaluation of pontine symptoms.

As to the cause of these hemorrhages, Moore and Stern agreed that increased intracranial pressure plays an important etiologic role, but stated the belief that if it were the only factor pontine hemorrhage should be much more frequent.

According to Erickson,[10] gross lesions of the hypothalamus or brain stem were present in 16 of 20 cases of neurogenic hyperthermia in which necropsy was per-

5. Wilson, G., and Winkelman, N. W.: Gross Pontile Bleeding in Traumatic and Nontraumatic Cerebral Lesions, Arch. Neurol. & Psychiat. **15**:455-470 (April) 1926.

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7. van Gehuchten, P.: Le mécanisme de la mort dans certains cas de tumeur cérébrale, Encéphale **2**:113-127 (Sept.-Oct.) 1937.

8. Jefferson, G.: Tentorial Pressure Cone, Arch. Neurol. & Psychiat. **40**:857-876 (Nov.) 1938.

9. Moore, M. T., and Stern, K.: Vascular Lesions in Brain-Stem and Occipital Lobe Occurring in Association with Brain Tumours, Brain **61**:70-98 (March) 1938.

10. Erickson, T. C.: Neurogenic Hyperthermia (A Clinical Syndrome and Its Treatment), Brain **62**:172-190 (June) 1939.

formed. The results of the experimental work of Keller and Blair [11] indicated that lesions of the brain stem produce a disturbance of the heat-regulatory mechanism.

Schwarz and Rosner [12] made a pathologic study of the brains in 100 cases of tumor of the brain. Herniation of the temporal lobe was present in 83 of the 100 cases. Gross examination disclosed fresh hemorrhages, of various sizes, within the brain stem in 19 instances. Microscopic examination revealed small hemorrhages in many other cases. The clinical findings were included in the article by these authors.

Scheinker,[13] in 1945, reported 55 cases of transtentorial herniation of the brain stem. He divided his cases into three groups according to the underlying pathologic conditions that were present. Group 1 included cases of cerebral vascular disease; Group 2, cases of cranial trauma, and Group 3, cases of space-occupying lesions. He found that edema and hemorrhage of the brain stem accompanied the herniation. In most of the cases the hemorrhage was situated in the gray matter of the rostral portion of the brain stem.

Carrea,[14] in 1944, noted hemorrhages of the brain stem in association with metastatic tumors within the cerebrum. Woodhall, Devine, and Hart [15]; Gurdjian and Webster [16]; Shenkin and Grant [17]; McKenzie,[18] and other authors have noted hemorrhages of the brain stem in association with meningeal bleeding.

Stopford,[19] in 1915, described the arterial pattern of the pons and medulla. The venous blood of the medulla apparently flows caudad into the venous plexus of the spinal cord, whereas the blood in the veins of the pons and mesencephalon flows cephalad. The superficial veins of the pons seem to join into lateral trunks, which continue as the superior petrosal sinus. Coursing around each cerebral peduncle is a rather large basal vein, which drains the mesencephalon and continues into the great vein of Galen (vena cerebri magna). The plexus of veins in the pia of the pons and mesencephalon is extensive. The basal vein seems to be the largest channel collecting blood from this plexus.

The results of angiographic studies give added support to the assumption that the venous blood of the rostral portion of the brain stem flows cephalad. Visuali-

11. Keller, A. D., and Blair, J. R.: Further Observations on the Distribution at Level of Pons of Descending Nerve Fibers Subserving Heat Regulating Functions, Am. J. Physiol. **147**:500-508 (Nov.) 1946.

12. Schwarz, G. A., and Rosner, A. A.: Displacement and Herniation of Hippocampal Gyrus Through Incisura Tentorii: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **46**:297-321 (Aug.) 1941.

13. Scheinker, I. M.: Transtentorial Herniation of Brain Stem; Characteristic Clinicopathologic Syndrome; Pathogenesis of Hemorrhages in Brain Stem, Arch. Neurol. & Psychiat. **53**:289-298 (April) 1945.

14. Carrea, R. M. E.: El edema agudo cerebral y las hemorragias mesencefálicas como causa de muerte en los tumores metastásicos, Arch. neurocir. **1**:228-235 (April-June) 1944.

15. Woodhall, B.; Devine, J. W., Jr., and Hart, D.: Homolateral Dilatation of Pupil, Homolateral Paresis and Bilateral Muscular Rigidity in the Diagnosis of Extradural Hemorrhage, Surg., Gynec. & Obst. **72**:391-398 (Feb.) 1941.

16. Gurdjian, E. S., and Webster, J. E.: Traumatic Intracranial Hemorrhage, Am. J. Surg. **75**:82-98 (Jan.) 1948.

17. Shenkin, H. A., and Grant, F. C.: Middle Meningeal Hemorrhage, Am. J. Surg. **75**:704-708 (May) 1948.

18. McKenzie, K. G.: Extradural Haemorrhage, Brit. J. Surg. **26**:346-365 (Oct.) 1938.

19. Stopford, J. S. B.: The Arteries of the Pons and Medulla Oblongata, J. Anat. **50**:131-164 (Jan.) 1916.

zation of the great vein of Galen may be obtained when dye is injected into the vertebral arteries, but not when it is injected into the carotid arteries.

MATERIAL AND METHOD OF STUDY

This report is based on a review of the clinical observations and postmortem findings in 122 cases of vascular lesions of the brain stem observed at the Mayo Clinic. In 51 of these cases, serial sections of the brain stem and hypothalamus were examined microscopically to establish more exactly the site and extent of the vascular lesions. In cases in which the underlying pathologic condition was an intracranial tumor, the site, type, and grade of malignancy of the tumor were ascertained.

RESULTS

The primary pathologic conditions in this group of 122 cases are listed in Table 1. Infarction secondary to vascular occlusion, as well as hemorrhage, was noted in the brain stem of patients who died of occlusion of the basilar artery or of a tumor of the posterior fossa. In 17 of the 20 cases of tumor of the posterior fossa the tumor was an acoustic neurilemmoma.

TABLE 1.—*Primary Pathologic Conditions in 122 Cases of Vascular Lesions of the Brain Stem*

Primary Pathologic Condition	Cases
Infratentorial lesions	42
Tumor of posterior fossa (20 cases)	
Thrombosis of basilar artery (17 cases)	
Primary pontine hemorrhage (3 cases)	
Pontine tumor (2 cases)	
Systemic disease or inflammation of central nervous system	11
Uremia (3 cases)	
Arsenic poisoning (2 cases)	
Meningitis (2 cases)	
Poliomyelitis (2 cases)	
Encephalitis (1 case)	
Leukemia (1 case)	
Supratentorial lesions	69
Cerebral tumor (27 cases)	
Cerebral hemorrhage (17 cases)	
Cerebral infarction (12 cases)	
Cranial injury (7 cases)	
Subdural hemorrhage without history of trauma (3 cases)	
Rupture of cerebral aneurysm (2 cases)	
Cerebral abscess (1 case)	
Total	122

Of the 122 patients, 84 were males and 38 were females. Cerebral infarction and thrombosis of the basilar artery were the most frequent causes of death in cases in which the patients were in the seventh to the ninth decade of life. In seven cases the patients were less than 20 years of age. The diagnosis in these cases was as follows: poliomyelitis, three cases; tumor of the posterior fossa, two cases; cranial injury, one case, and arsenic poisoning, one case. One patient had a primary pontine hemorrhage of unknown origin.

Although I was interested in the clinical syndrome common to the three main groups of pathologic conditions, my chief concern was with the cases of supratentorial lesions, in which the hemorrhage of the brain stem occurs secondary to or in association with a supratentorial space-occupying lesion (Figs. 1, 2, 3, and 4). The hemorrhages in these cases were found in the pons and mesencephalon. Gross examination did not disclose extension of the hemorrhage above the tentorium or below the caudal border of the pons.

Hemorrhage may occur in any portion of the mesencephalon and pons but is seen most frequently in the tegmental, or dorsal, portion. In many cases in this

series the hemorrhage appeared to extend in the direction of the surrounding fiber tracts; in some cases, however, it followed the course of penetrating vessels. In most cases it was not possible to determine whether the hemorrhages followed nerves or vessels.

In cases in which examination disclosed unilateral grooving of the basis pedunculi by the border of the tentorium cerebelli, the hemorrhage within the brain stem was situated on the side of the grooving and caudal to it (Fig. 5).

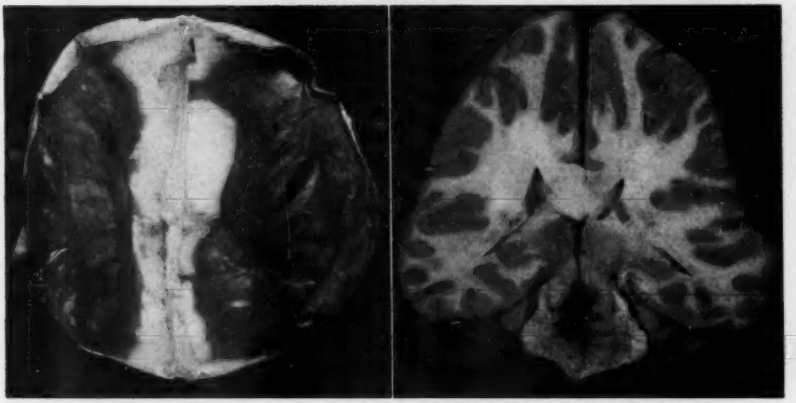

Fig. 1.—Bilateral subdural hematoma with hemorrhage into the brain stem.

Fig. 2.—Cerebral hemorrhage with hemorrhage into the brain stem.

Cerebral edema was apparent in all cases of supratentorial tumor, abscess, hemorrhage, or infarction. Herniation of a portion of the temporal lobe through the tentorial notch was a frequent finding.

Microscopic study of sections taken through the pons and midbrain revealed, in addition to the hemorrhages of varying sizes, generalized engorgement of veins and capillaries and edema of the surrounding tissue. The hemorrhage was situated within the region of the brain stem, from the level of the tentorium to the caudal border of the pons, and seldom extended beyond these boundaries. The dorsal portions of the pons and mesencephalon were involved much more frequently than the more

ventral parts. The reticular matter and the periaqueductal gray matter were the common sites of the hemorrhages.

In the analysis of the clinical course, an attempt was made to find clues which would help in the diagnosis of a lesion of the brain stem. Sudden or rapidly develop-

Fig. 3.—Cerebral abscess with hemorrhage into the brain stem.

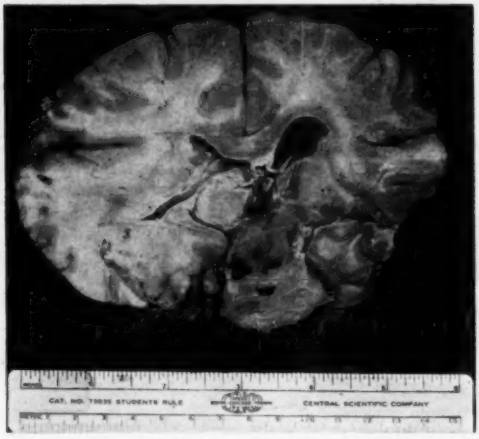

Fig. 4.—Cerebral tumor with hemorrhage into the brain stem.

ing coma, progressive neurogenic hyperthermia, extreme tachycardia, and rapid, difficult breathing were common symptoms in this series of cases. These symptoms were common to all three groups of primary pathologic conditions.

A changing state of consciousness was noted in 113 of the 122 cases. Profound coma was of sudden onset in 48 of the 113 cases. It developed rapidly, within two or more hours, in 34 cases. Coma was continuous after operation in 29 cases and coincident with trauma in 2 cases.

In most of the cases changes in the temperature, pulse, and respiration occurred soon after the onset of coma. The temperature was recorded in 103 cases (Table 2). In 65 (63%) of these cases the temperature increased to 103 F. or more. In most of the 65 cases, it continued to increase to between 104 and 107 F. Sweating was absent; the extremities were icy, and the trunk was abnormally warm in the cases in which hyperthermia occurred. In contrast with these cases were the seven in which the temperature remained well below normal.

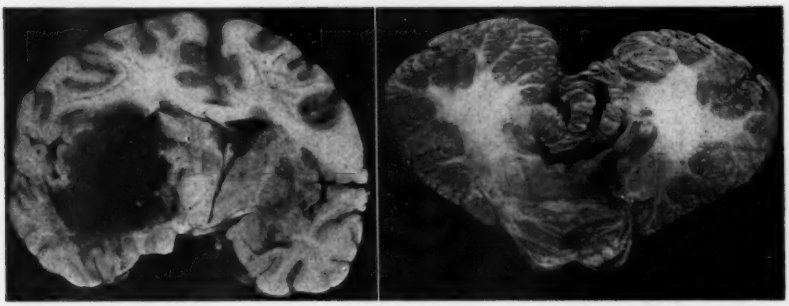

Fig. 5.—Hemorrhage into the brain stem on right side with cerebral tumor on left side.

TABLE 2.—*Changes in the Temperature, Pulse, and Respiration in Cases of Acute Vascular Lesions of the Brain Stem*

Temperature, Degrees (F)	Cases	Pulse, Beats per Min.	Cases	Respirations per Min.	Cases
Above 103	65	More than 110	73	More than 22	76
Less than 98	7	Less than 65	13	Less than 12	5
98 to 103	31	65 to 110	21	12 to 22	17
Totals	103*		107*		98*

* These figures represent the respective number of cases in which the temperature, pulse rate, and respiratory rate were recorded.

The pulse rate was recorded in 107 cases. In 73 (68%) of these cases, the pulse rate was faster than 110 beats per minute, and usually was 140 or faster. In many of these cases, the pulse rate initially was slow, but tachycardia developed later. In 13 of the 107 cases the pulse rate remained below 65 a minute until death occurred.

Observations on the respiration were recorded in 98 cases. In 76 (78%) of these cases, the respiratory rate was abnormally rapid. In more than half of the 76 cases the respiratory rate was 40 or more per minute. Other respiratory abnormalities were observed in 36 of the 98 cases. The most frequent of these was Cheyne-Stokes respiration, which was observed in 26 of the 36 cases. In the 10 remaining cases, the breathing was stertorous, shallow, irregular, or of the Kussmaul type. Cyanosis of rather intense degree was evident in 33 of the 98 cases.

Other signs and symptoms which were observed in this series of 122 cases are listed in Table 3. Many of these signs and symptoms were suggestive of the presence of a lesion of the brain stem.

Convulsive movements, ranging from isolated twitching in an extremity to generalized seizures, occurred simultaneously with the onset of changes in the vital signs in about one-fourth of the cases.

The time of onset for the vascular lesion in the brain stem could be inferred in 97 cases on reviewing the histories. The duration of life after onset of characteristic symptoms and signs of vascular lesions of the brain stem is shown in Table 4.

Twenty-seven cases in which supratentorial tumors were associated with hemorrhage of the brain stem were studied with reference to the diagnostic and surgical

TABLE 3.—*Supplementary Signs and Symptoms in 122 Cases of Acute Vascular Lesions of the Brain Stem*

Signs and Symptoms	Cases
Convulsive movements	32
Hemiplegia	28
Pupillary changes	26
Paralysis of cranial nerves	21
Headache	20
Vomiting	16
Falling	14
Confusion and agitation	6
Crying out	4
Somnolence	3
Hiccup	3
Paresthesia	3
Decerebrate rigidity	2
Euphoria and laughing	2
Blindness	2
Tremor	2
Yawning	1

TABLE 4.—*Duration of Life After Onset of Acute Vascular Lesions of the Brain Stem*

Time of Death, After Onset of Symptoms	Cases
Within 24 hr.	43
Between 24 and 72 hr.	29
Between 72 hr. and 2 wk.	25
Total	97

procedures employed. The average age of patients in this group was 50.6 years. Twenty-one of the 27 patients were males.

It is interesting to note the diagnostic and surgical procedures which were carried out in 21 of the cases of supratentorial tumors and hemorrhages of the brain stem. In four cases lumbar puncture alone was performed. Pneumoencephalography or pneumoventriculography was carried out in seven cases, in each of which a craniotomy was subsequently performed. In 11 cases a needle biopsy was performed, and the presence of a tumor was verified in 7 cases. In 5 of these 21 cases tumors of the brain were removed surgically.

Figure 6 shows the histologic type, the grade of malignancy, the site of the cerebral tumor, and the extent of hemorrhage in the brain stem in 20 cases.

It will be seen that the malignant gliomas of the frontal and temporal lobes were associated most frequently with hemorrhage of the brain stem. In only 1 of the 20

cases (Case 13) did the hemorrhage extend above the level of the tentorium and into the hypothalamus. In this case the tumor itself had extended from the left temporal lobe into the region of the hypothalamus.

COMMENT

The results of this study suggest that the syndrome most characteristic of an acute vascular lesion of the rostral portion of the brain stem consists of the sudden onset of coma, hyperthermia, tachycardia, and rapid, difficult breathing. The patient's condition deteriorates steadily, and death invariably occurs. In the series studied

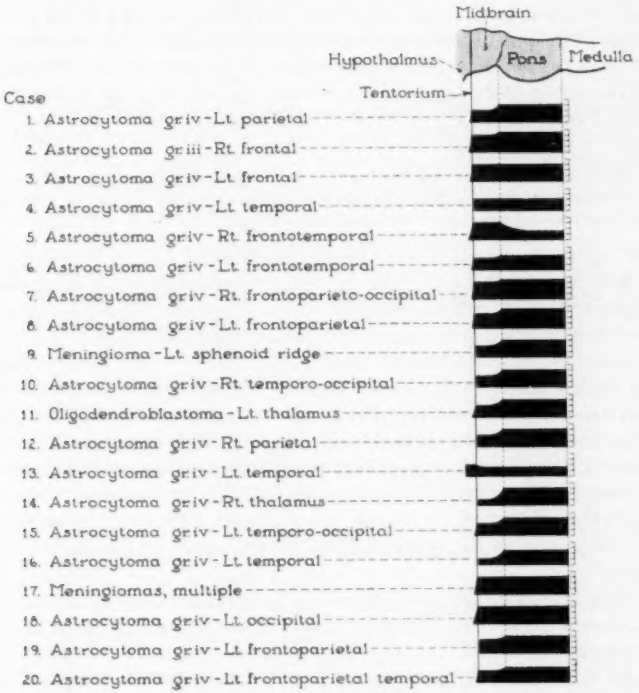

Fig. 6.—Correlation of histologic type, grade of malignancy, and site of cerebral tumor with extent of hemorrhage in the brain stem in 20 cases. The estimated degree of hemorrhage in the brain stem is represented by the width of the black line. For example, Case 14 represents near-complete involvement of the pons with hemorrhage, little involvement of the midbrain, and no hemorrhage in the hypothalamus.

this syndrome was present even when other lesions of the brain and meninges existed. The results of this study, therefore, suggest that hemorrhage into the brain stem often is the cause of death in cases of brain tumor, meningeal hematoma, cerebral abscess, and cerebral hemorrhage. The evidence indicates that hemorrhage of the brain stem complicating supratentorial tumor, hemorrhage, or abscess may be diagnosed prior to death. Recognition of the typical signs and symptoms is definitely possible.

That paradoxical pyramidal signs, decerebrate rigidity, imbalance of the extraocular muscles, and pupillary changes are manifestations of tentorial herniation has been established by Jefferson [8] and by Schwarz and Rosner.[12] The more profound changes in the vital signs may also be encountered in cases of tentorial herniation. However, deep coma, hyperthermia, tachycardia, and rapid, difficult breathing usually occur in cases of hemorrhage in the brain stem. Tentorial herniation and bleeding into the brain stem coexisted in most of the cases of supratentorial space-occupying lesions. Dysfunction of the brain stem may precede the actual hemorrhagic lesions in cases in which compression and obstruction to the flow of blood are present.

I was surprised to find that convulsive movements ushered in the onset of the changes in vital signs in about one-fourth of the 122 cases. The seizures varied in severity from isolated twitching in one extremity to grand-mal convulsions.

Nothnagel,[20] in 1868, suggested that convulsions may originate in pontine centers. However, Dana,[1] in 1903, rejected Nothnagel's hypothesis with the following statement:

> In lesion of the pons, there are practically never any convulsions, due, at least, directly, to this lesion. When onset is quite acute, and softening involves the ventral part of pons and fibers of motor tract, there may be some trembling and twitching.

Neurologists in general have followed Dana's belief. Recently the observations of neurophysiologists have brought to light the possibility that subthalamic and mesencephalic centers influence cortical action potentials. Their discovery of the inhibitory and facilitatory mechanisms of the reticular formation of the brain stem also directs attention to the brain stem as an important center for motor control. In cases of cortical lesions simultaneous damage to the reticular matter of the brain stem may be sufficient to initiate convulsions through a synergistic effect. Another possibility, however, exists, especially in cases in which the convulsive seizure is generalized. During such a seizure there is probably a substantial rise in intracranial venous pressure. This may lead to hemorrhage into the brain stem, already damaged by compression, distortion, or venous stasis. Under these circumstances, the convulsive seizure may be the cause, rather than the result, of the lesions within the brain stem.

Van Gehuchten's report [7] was important in limiting the use of lumbar puncture in cases of cerebral tumor. My observations in cases in which tumor of the brain was complicated by hemorrhage into the brain stem indicate further need for caution in the use of surgical diagnostic procedures, such as lumbar puncture, pneumoencephalography, ventriculography, and needle biopsy.

The results of this study suggest that acute vascular lesions of the brain stem produce a clinical picture which may be recognized prior to death. A study of the site of the hemorrhage in cases of supratentorial space-occupying lesions suggests that the hemorrhage is the result of, or associated with, venous stasis caused by interference with the return of blood from the rostral part of the brain stem into the system of Galen. The interference with the return of venous blood probably occurs at the level of the tentorium cerebelli.

There also is indication that acute lesions within the brain stem may give rise to disturbances in the autonomic nervous system not unlike those caused by hypothalamic dysfunction.

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20. Nothnagel, H.: Die Entstehung allgemeiner Convulsionen vom Pons und von der Medulla oblongata aus, Arch. path. Anat. **44**:1-12, 1868.

OBSERVATIONS ON EFFECT OF CORTICOTROPHIN IN SCHIZOPHRENIA

A Preliminary Report

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RECENT investigations by Hoagland and Pincus [1] have emphasized the defective physiological responses of the schizophrenic patient to adrenocortical stimulation. Altschule and co-workers [2] have reported essentially normal physiological responses to corticotrophin in schizophrenic patients, with the exception of suggestive greater-than-normal changes in glucose tolerance. In an attempt to evaluate the relationship between adrenocortical activity and the psychological state, we administered corticotrophin in large doses to six patients (three men and three women) with schizophrenia. Significant data concerning these patients are presented in the accompanying table.

All the patients were observed in a control period varying from two to four weeks before the administration of the corticotrophin. The influence of placebos and other drugs, such as amobarbital (amytal®), *d*-desoxyephedrine hydrochloride (pervitin®), amphetamine, and mescaline, was studied during the control period, or after a suitable time had elapsed after the corticotrophin was discontinued. The corticotrophin [3] was given intramuscularly, four injections every six hours, to make up the daily dose of 100 to 200 mg. for 10 to 30 days. Laboratory studies included weekly electroencephalographic recordings and determination of blood electrolytes (sodium, potassium, carbon-dioxide-combining power, chlorides), sugar, and circulating eosinophils.[4] The patients were obseved then for at least two weeks after the cessation of corticotrophin administration.

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1. Hoagland, H., and Pincus, G.: Pituitary-Adrenocortical Function in Patients with Severe Personality Disorders, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, pp. 544-553.

2. Altschule, M. D.; Promisel, E.; Parkhurst, B. H., and Grunebaum, H.: Effects of ACTH in Patients with Mental Disease, Arch. Neurol. & Psychiat. **64**:641-649 (Nov.) 1950.

3. The corticotrophin was supplied through the courtesy of Dr. John R. Mote, Medical Director, The Armour Laboratories.

4. Randolph, T. G.: Differentiation and Enumeration of Eosinophils in the Counting Chamber with a Glycol Stain, J. Lab. & Clin. Med. **34**:1696-1698, 1949.

GENERAL OBSERVATIONS

The somatic effects of the corticotrophin were not unusual and seemed to be related to the dosage factor. Acne appeared in all three female patients, and not in the male patients. All patients showed a normal eosinopenic response to an injection of 25 mg. of the hormone (Table). The effects on the blood sugar and blood electrolytes and on the water balance were within the range seen in normal subjects. Five patients showed the development of diffuse slow activity in the electroencephalogram correlated with corticotrophin administration, as reported previously.[5]

Only one patient (Case 3) showed notable psychological changes. This woman, aged 23, with a four-year history of progressive social withdrawal and with ideas of reference, influence, auditory hallucinations, and disturbed behavior for about one year, was given 100 mg. of corticotrophin a day for 30 days. In this time she became more negativistic, depressed, and hostile. During the day following the last dose of corticotrophin, she became even more negativistic and agitated and had more

Effect of Corticotrophin in Patients with Schizophrenia

Case	Age	Sex	Diagnosis	Duration of Psychosis, Yr.	Dose of Corticotrophin		Duration of Drug Administration, Days	Eosinophil Response (% Fall)*	Somatic Effects	Electroencephalographic Changes	Psychological Changes
					Mg./Day	Total (Mg.)					
1	39	F	Schizophrenia, pseudoneurotic	4	200	2,000	10	90	Water retention; weight gain; acne	—	Increased anxiety, related to somatic effects
2	23	F	Schizophrenia, unclassified, with depressive features	6	200	2,000	10	96	Slight acne	+	None
3	22	F	Schizophrenia, mixed	1	100	3,000	30	85	Acne; slight water retention	+	Catatonic episode after corticotrophin was discontinued
4	24	M	Schizophrenia, hebephrenic	6	100	1,500	15	75	None	+	None
5	25	M	Schizophrenia, paranoid (catatonic features)	4	100	3,000	30	90	None	+	None
6	23	M	Schizophrenia, unclassified	4	100	3,000	30	70	None	±	None

* Measured four hours after the first injection of 25 mg. of corticotrophin. The Randolph method [4] was used.

intense delusions, hallucinations, and stereotypy. She became more withdrawn and out of contact and stated that she was dead. This was regarded as a catatonic episode occurring in the course of her schizophrenic reaction. This state persisted, with diminution of severity, for one month, at which time the patient was placed on insulin therapy. This treatment had no significant effect on her symptoms. It was believed that the physiological stress of the hyperadrenal state, particularly the metabolic imbalance of the withdrawal period, exaggerated an already present mental trend. Actually, she had incorporated the treatment situation into her bizarre delusional system. The reaction of this patient is quite similar to that seen in recent cases of psychotic reactions induced by corticotrophin or cortisone.[6] In

5. Hoefer, P. F. A., and Glaser, G. H.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy: Electroencephalographic and Neuropsychiatric Changes in 15 Patients, J. A. M. A. **143**:620-624 (June 17) 1950.

6. Glaser, G. H.: Psychotic Reactions Induced by ACTH and Cortisone, in preparation, 1951.

certain of these patients, but not in all, latent psychotic or prepsychotic personality trends became manifest during or immediately after cessation of the corticotrophin or cortisone therapy.

Anxiety was increased in one patient in relation to the somatic effects of the gain in weight due to water retention, and the appearance of acne (Table).

No patient showed changes which could be regarded as beneficial. No euphorizing effect was noted, and no depressive tendency was altered.

CONCLUSIONS

Although this series of cases is a small one, we feel that these essentially negative observations are significant. Excessive stimulation of the adrenal cortex and induction of the hyperadrenal state in these schizophrenic patients did not bring about any beneficial psychological changes. The possible effect of exaggeration of certain psychotic tendencies is noted.

AMNESIA—ITS INTEGRATIVE ANALYSIS IN PSYCHOPATHOLOGICAL ORIENTATION

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THE PECULIAR behavioral patterns met with in the psychoses, associated personality disorders and/or the neuroses, possess individualized connotations and bear a specific relation to the settings in which they have occurred. Of notable significance is the investigation of impairment of memory as a disturbance of higher mental expression.

Etiologically, this derangement may be the concomitant of destructive physical or chemical alterations of cortical neurons or may follow (as an automatic recourse) as a defense pattern resorted to by the neurotic patient in an effort to conceal the truth from himself. This he does in order to attain emotional gratification or easement, though it may disregard reality, even to the point of becoming objectionable to those in his environment, or may culminate in personality impairment.

The increasing attention to mental disturbances and their recognition as the neuropsychiatrist's responsibility, as evidenced in the current psychiatric literature, led to the present study of the complexities of the memory states.

The absence of memory or its inhibition has its many facets; these, as such, will be considered later and their elements in both functional and organic psychiatric states evaluated.

As the neuropsychiatrist is, in the nature of things, called upon in medicolegal and in other settings to interpret differentially states of amnesia, to fixate their specific organic or psychogenic existence, and to determine the consequences thereof, he should properly commence every inquiry into the course of any amnestic situation with a complete neurological work-up in order to determine the presence, extent, or absence of structural or toxic alterations in the higher cortical centers. Collaterally, and of equal importance, is an all-inclusive, long-range psychobiological study calculated to disclose the constitutional character of the patient's preamnestic assets, together with the appraisement of the examinee's psychic integrity.[1]

The reception, preservation, and presentation to the consciousness of previously acquired mental impressions is the domain of memory. It serves to adjust the person to advantageous conformation to his environment, and its processes are constantly and unconsciously drawn upon to achieve psychobiological adaptation to external

1. (*a*) Whitehorn, J. C.: Guide to Interviewing and Clinical Personality Study, Arch. Neurol. & Psychiat. **52**:197-216 (Sept.) 1944. (*b*) Gillespie, R. D.: Clinical Differentiation of Psychogenic and Physiogenic Disorders, Brain **51**:254-275, 1928. (*c*) Myerson, A.: Neuroses and Neuropsychoses: Illustrative Case Histories, Am. J. Psychiat. **94**:961-983, 1938. (*d*) Siegal, L. J.: Psychodynamic Patterns and Their Implications on the Neuropsychic Entities, Dis. Nerv. System **9**:308-314, 1948.

stimuli. It is on the basis of the mental material presented, therefore, that the neuropsychiatrist is called upon for an integrative determination of existing amnestic dynamics and their symbolic identity. Although persons with neurological, as well as organic (toxic, degenerative, or traumatic), illness may present an amnestic state, their impairments connote specific qualitative and quantitative attributes, which shall be traced.

AMNESTIC VARIATIONS IN THE PSYCHIC STATES

1. The neurotic's memory lapse, which most frequently is completely and abruptly regained, is predicated upon convenience; i. e., the patient will choose the situations which he wishes to blot out from consciousness. Emotional conflicts involving such factors as shame, guilt, inferiority, or insecurity are productive of psychological pain, the memory of which threatens one's self-esteem. When such associations are repressed, by their being driven below the threshold of awareness, they are temporarily blotted from memory. By this process of banishing recollection of the agonizing experience, it becomes part of the patient's unconscious psychological processes, the return of the intolerable emotional feeling being thus prevented and psychological wholeness maintained.[2]

2. The organically ill patient, on the other hand, if his memory returns at all, will regain it by degrees, or his condition will often terminate in permanent memory impairment. Such deficiencies of retentivity occur in the encephalopathies resulting from neurological post-traumatic defects, the degree of memory impairment depending upon the extent of cerebral damage, as well as upon location of the injury.[3]

3. The incomplete and haphazard types of amnesia (as to personal identity and nonpersonal matters) found in dementia paralytica and the senile psychoses have their source in organic cortical changes.[4]

4. On the other hand, loss of memory function for definite or limited events covering particular periods may be caused either by structural changes in the higher cortical neurons or by the presence of psychogenic elements. In my services at the hospital bedside, in the outpatient department, as well as in consultative settings, I have repeatedly observed relevant examples of this category of memory erasures. They characteristically present themselves in situations following unsuccessful suicidal attempts by ingestion of an overdose of a drug, or after epileptic seizures, electric shock therapy, or syncopal attacks.[5]

5. In the mentally deteriorated patient whose illness is etiologically predicated upon toxic or degenerative alterations of the higher cortical centers ascribable to irrecoverable destructive lesions, intelligence and perception are the first to fade;

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2. (*a*) Lennox, W. G.: Amnesia, Real and Feigned, Am. J. Psychiat. **99**:732-743, 1943. (*b*) Gillespie.[1b] (*c*) Parfitt, D. N., and Gall, C. M. C.: Psychogenic Amnesia: The Refusal to Remember, J. Ment. Sc. **90**:511-527, 1944, (*d*) Siegal.[1d]

3. (*a*) Siegal, L. J.: Craniocerebral Postconcussive Personality States, Psychiatric Quart. (Supp.) **24**:65-72, 1950. (*b*) Strauss, I., and Savitsky, N.: Head Injury: Neurologic and Psychiatric Aspects, Arch. Neurol. & Psychiat. **31**:893-955 (May) 1934.

4. (*a*) Moore, M., and Solomon, H. C.: Contributions of Haslam, Bayle, and Esmarch and Jessen to History of Neurosyphilis, Arch. Neurol. & Psychiat. **32**:804-839 (Oct.) 1934. (*b*) Rothschild, D.: The Clinical Differentiation of Senile and Arteriosclerotic Psychoses, Am. J. Psychiat. **98**:324-333, 1941.

5. Curran, F. J.: Current Views on Neuropsychiatric Effects of Barbiturates and Bromides, J. Nerv. & Ment. Dis. **100**:142-169, 1944.

and as the process advances, progressive impoverishment of memory supervenes. The latter deficiency is attributable to the subject's inability to combine logically his previously lived-through situations with those of the present time. In investigating the clinical characteristics of patients with deteriorative mental changes—the dementias of syphilitic, degenerative, arteriosclerotic, neoplastic, toxic, or inflammatory origin; and those complicating nutritional deficiencies, incidental to epilepsy, or following cerebral trauma—I have been intrigued by the progression of the amnestic morbid consequences. First to go is the ability to remember recent occurrences, and as the pathological process progresses, retention of remote happenings also fades. Finally, as the comprehension of any identifiable concrete entity can be had only through its integrative association with the memory thereof, the now extensive dissolution of the latter creates the further interrelated dysfunction of disorientation for time and place sense—hence the complete inability to take correct cognizance of person, location, or time.[6]

6. The amnesia experienced by one who has suffered a head concussion, whenever such trauma is followed by a variable interval of unconsciousness, may be of two types: (*a*) First, the patient is unable to remember the specific experience and time when the injury took place, and at times will also remain amnestic for an indeterminate period prior to the traumatic event. It is to be borne in mind, also, that after recovery from the blow to the skull the actual traumatic episode is never recalled once the consciousness has been lost, irrespective of the length of the period of this unconsciousness. If, in addition, loss of memory also exists for events which took place immediately before the blow to the skull occurred, such amnesia indicates that the higher integrative cortical functions have suffered as a result of the trauma. This want of recall has been expressed as retrograde amnesia. (*b*) If, on return to consciousness, the traumatized patient appears bewildered or experiences a blunting of awareness, the latter will invariably be followed by a blotting out of the memory for such bewildered or clouded period. This memory gap has been variously expressed as anterograde or post-traumatic amnesia. I have observed frequently that during their hospitalization after head trauma of various gradations such patients exhibit a chain of symptoms, which include disorientation for time and place, memory defect for recent occurrences, happenings antedating the trauma, and confabulations. The last, which are pure and inconsistent fabrications, are indulged in in order to fill in memory gaps and are in reality defensive untruths employed as an avoidance to admission of memory deficiency. This symptom pattern, known as the amnestic-confabulatory syndrome, and also called Korsakoff's syndrome, should not be mistakenly associated with Korsakoff's psychosis—an account of which appears below, within its proper classificatory division.[7]

EXPLORATION OF PSYCHOGENIC DISORDERS OF RETENTIVITY

The method adopted by the patient in his endeavor to cope with his state of anxiety will fixate the pattern of his neurotic condition. If his anxiety is severe enough, and amnesia supervenes, he will be unable to recognize matters relating to

6. (*a*) Kanzer, M.: Personality Disorders with Brain Tumors, Am. J. Psychiat. **97**:812-830, 1941. (*b*) Moore and Solomon.[4a] (*c*) Rothschild.[4b] (*d*) Siegal.[8a]

7. (*a*) Brock, S.: Injuries of the Skull, Brain and Spinal Cord, Baltimore, Williams & Wilkins Company, 1943. (*b*) Siegal.[8a] (*c*) Strauss and Savitsky.[3b]

his own personality, i. e., unable to identify himself by name; nor will he be able to account for his presence in new surroundings or identify the place he finds himself in.[8]

If it is an anxiety which transitively overcomes his total emotionality, the severity thereof may result in a hysterical dissociation, which, among other mechanisms, may consign the patient to flight automatism (fugue), with loss of memory both as to his past experiences and as to his identity. By this escape, his symptoms supply him, without consciousness on his part, with some semblance of solution for his difficulties and also serve to cushion his anxiety in his disturbed situation. His amnestic state, particularly, blots out memories for certain periods, whether brief or protracted, during which distasteful situations, e. g., horror, embarrassment, unrequited affection, or equally disturbing circumstances, had taken place.[9] Since the multitudinous inconstant collateral symptoms incident to the varying anxiety patterns are not the purport of this study, no attempt will be made to categorize them here, but they may be examined elsewhere.[1d] But the psychic release resulting in an amnestic state, which is the expression of an escape induced by personal emotional circumstances and carried out as a sudden retreat without conscious direction, merits attention here as a psychic peculiarity. In this flight (fugue) state, an amnestic gap may extend from hours to days to months. It is a form of hysteria in which conscious activity is of a restricted type, in which no thought regarding consequence of action is demonstrable, and in which all that is apparent is the patient's drive to escape from a distressing psychological situation. Although such a sufferer oftenest realizes his own identity, he cannot account for or remember how he has come to find himself in some presently strange location and is equally unable to recall wandering away from his customary environment.[10]

In order to round out consideration of the remaining types of memory block met with in the category of functional amnesia, the somnambulist's pattern requires evaluation. In his dreamlike fugue state, in which consciousness is partially or wholly suspended, and which resembles sleep, the patient carries out, with his eyes open, a variety of complex acts, none of which he is able to remember upon awakening. During the somnambulistic trance and while in his automatic wandering, he avoids any obstructions in his path, appears to have a definite aim, and will frequently reply to questions or obey directions automatically. Such somnambulistic performances are representative of longed-for efforts to satisfy impulses which were entirely repressed by the patient during his waking state because of their dreaded and disagreeable content.[11]

Finally, another form of fugue memory gap in the foregoing functional (psychogenic) category is infrequently encountered in the hysterical patient who may exhibit a dual personality. This is more complete dissociation than somnambulism, and here the behavior patterns will reveal mutual exclusiveness of individuality, characterized by inability to recall during one personality cycle what had occurred during the other. Psychologically, the patient is unable to select between two or

8. Lennox.[2a] Parfitt and Gall.[2c] Siegal.[1d]

9. Stengel, E.: On the Etiology of the Fugue States, J. Ment. Sc. **87**:572-599, 1941.

10. Lennox.[2a] Parfitt and Gall.[2c] Stengel.[9]

11. Sadger, J.: Sleep Walking and Moon Walking, New York, Nervous & Mental Disease Publishing Company, 1919.

more conflicting behavioral goals, and in this frustrating situation he assumes the more tolerable personality, while the opposing one is kept in suppression. The curbed material, originally appearing to the patient as being against his natural mental and emotional inclinations, has acquired enough systematic correlation to establish a supplementary and independent self. Axiomatically, the condition may be psychologically expressed as a "double mind working to contrary purposes" (Jekyll and Hyde).[11a]

Malingering may be mistaken for hysteria and is ofttimes so treated. The causes for its assumption are manifold. Etiologically, frustrations of dynamic requirements, sensations of insecurity, and environmental bewilderment are among the basic elements which may precipitate the motivation. Among the more immediate causes, the ones commonly met with are desire for financial advantage, escape from onerous undertakings, fear of punishment, dread of physical injury, fear of loss of life, or fear of exposure to social or financial ruin.

The malingerer, whom I consider a pathological personality type, will exhibit such voluntary acts as complete simulation of an illness or injury, or, if he chances to have any kind of mild symptoms, he will overstate the condition beyond truth or medical reason therefor in order to establish a "disabling" incapacity, or he will falsely impute causality of any disordered bodily function of which he may be suffering to the acts of another, for the purpose of fraudulently affixing responsibility for damages for his disability on the guiltless one whom he has selected as the scapegoat. The incentive for the malingerer's act is a premeditated conscious desire to produce symptoms in order to deceive, with no wish to be relieved of his symptoms, together with an exhibited fear of being examined. His response reaction is guarded and is combined with mistrust, as well as elusiveness. It is worthy of special diagnostic note to observe that the foregoing elements are directly antithetical to those found in the psychoneuroses, and the psychodynamics of this consciously directed deviate behavior will serve to evaluate and diagnostically to separate the malingerer from the frankly psychoneurotic patient's demonstrable dynamic releases (*q. v.*).

On the basis of these criteria, it is of probative value to study the suspected malingerer by directing him, while he is unaware, and his attention is diverted, to perform an unanticipated act with the bodily part claimed by him to be incapacitated. He may also be subjected to sudden distraction by a startling or alarming utterance, which will unwittingly cause him to use his supposedly immobile body or some pretendedly implicated part thereof. Such a patient, when under close clinical scrutiny for some definite period, will invariably give himself away by not maintaining his symptoms when he believes he is no longer observed. While caught off his guard, the malingerer will unwittingly reveal minor contemporaneous incidents, such as had taken place with, or during, the particular situation of which he pretends to have no memory. When the threatening situation sufficiently overwhelms him, the malingerer acts out his amnestic mechanisms anticipatory to avoidance of the cruel or threatening consequence. As it is such feared memories that he desires to blot out, he will also exhibit a loss of memory

11a. Franz, S. I., and Gordon, K.: Psychology, New York, McGraw-Hill Book Company, Inc., 1933.

for his own personal identity.[12] It is well to bear in mind that feigned symptoms usually appear precipitately.

EXPLORATION OF NONTRAUMATIC ORGANIC DISORDERS OF RETENTIVITY

Although the patient's behavior frequently presents variable overlapping of symptoms, their significance is founded upon proper etiological consideration. In organic memory impairment the disintegration is insidious, is indefinitely progressive, and will depend for its severity upon the extent of structural or toxic neuronal alterations.

The memory defect of the patient with early dementia paralytica shows loss of retentive ability for recent events, as well as inability to remember persons, either by their names or when they appear before him. Etiologically, the dysfunction is the result of a diffuse syphilitic meningoencephalitis, involving the brain and the spinal cord, with degenerative changes, which run a chronic progressive course.

The amnesia met with in Korsakoff's psychosis is both retrograde and anterograde and can extend to marked impairment of memory for events which may have taken place even a few minutes before their actual occurrence. The most significant symptom in this psychosis is the patient's inability to remember present nonpersonal experiences, coupled with inability to identify persons before him or to associate his own relation to his locale. In addition, in their attempt to fill in memory gaps, I have, on numerous occasions, observed such patients confabulate freely by glibly reciting fabricated imaginary accounts of their activities. Frequently after recovery, however, I have seen memory regained for events which were not remembered during the psychotic syndrome. This condition occurs as a sequel to chronic alcoholism and has been identified by its more descriptive pathological nomenclature of polyneuritic psychosis. Thalamic alterations, cerebral edema with neuronal lipochromatosis, polyneuritis, wrist and foot drop, and abolition of deep reflexes are among the outstanding impairments included in this psychotic disorder—met with in long-range drinkers.

It should be noted at this juncture, however, that the foregoing clinical picture of memory dysfunction, together with confabulatory disturbances, will also be encountered, among other of the abnormalities of mental activity, in patients with brain tumor. As the onset of memory disorganization in these patients is usually insidious, except with the fast-growing gliomas, amnestic and confabulatory symptoms cannot be considered dependable from the standpoint of early diagnostic or localizing value. It might not be amiss to point out that the location of neoplasms productive of the foregoing psychotic confabulations and memory defects is most frequently above the tentorium. Ultimately, the over-all historical and neurological components will require careful scrutiny in such cases in order to avoid a hasty diagnostic error of Korsakoff's psychosis.[13]

The memory disorder in cerebral arteriosclerosis is rarely seen in patients younger than 50. In this condition, I have observed loss of recollection for recent

12. (*a*) Lennox.[2a] (*b*) Ossipov, V. P.: Malingering: The Simulation to Psychosis, Bull. Menninger Clin. **8**:39, 1944.

13. Bowman, K. M., and Jellinek, E. M.: Alcoholic Mental Disorders, Quart. J. Stud. Alcohol **2**:312-390, 1941. Kanzer.[6a] Knight, R. P.: Psychodynamics of Chronic Alcoholism, J. Nerv. & Ment. Dis. **86**:538-548, 1937.

events, which subsequently progresses to inability to remember names or faces. As the pathological process advances, amnesia becomes so complete that generalized disorientation supervenes. The organic damage responsible for this memory deficiency is sclerosis of the cerebral blood vessels, atrophy of the neuronal elements, and disseminated areas of softening.

Of similar characteristic quality is the amnesia encountered in patients with senile psychosis. The point of difference, however, is that memory dysfunction in such patients will not show up much before the age of 60, and more frequently I have seen it set in not much before the age of 70, or even later. Here, again, memory loss first takes place for recent happenings; and, as the psychosis progresses, the memory becomes completely disorganized and disorientation absolute. At necropsy there are demonstrable cerebral atrophic alterations, with cellular degeneration and senile plaque formations.[4b]

The amnesia of the patient with grand mal epilepsy is complete for the occurrence of the seizure. On awakening therefrom after a protracted sleep, such a patient, when asked, readily indicates recognition of a seizure occurrence by the feeling of generalized exhaustion from the tonic and clonic contractions to which the limb musculature had been subjected, the bitten tongue, and/or the postseizure bodily injuries, if any, which had been sustained during the epileptic attack. The cerebral pathology is inconstant, and at necropsy I have observed it to range all the way from no discernible lesions to ventricular deformation, cerebral atrophic changes, and meningeal adhesions.

On the basis of my own observations, I am in accord with H. H. Jasper that electroencephalographic tracings alone are not sufficiently dependable for determination of epilepsy, since many patients who show no clinical evidence of epileptic seizures nevertheless produce characteristic electroencephalographic records.[14]

The encephalopathies of veteran pugilists are the aftermath of repeatedly suffered trauma. Here, one is confronted with a symptomatology characteristic of progressive mental deterioration which had resulted from the patient's having suffered repeated blows about the head and face. This periodic shaking up of the brain substance, either through direct forcible impact or by way of contrecoup, is productive of histopathological alterations, with varying gradations of permanent, irreversible reduction in cerebral activity. The robust pugilist can usually undergo fistic punishment for four or five years, after which progressive impairment of his dexterity and speed follows in consequence. Concomitantly, mental and physical slowing up supervenes; awareness becomes clouded; variable bouts of confusion occur, and the gross demeanor typifies actions not unlike those seen in persons who are partially inebriated—hence the appropriate synonym "punch-drunk." Deficiencies of memory, as to both recent and past events, occur, and, coupled with this lack of ability to recall, capacity for concentration wanes commensurately. The cerebral defects which give rise to the permanence of this amnestic condition are hemorrhages of the small cerebral and meningeal vessels and parenchymatous scarring. In addition, a breaking up of ganglion cells and their fibers also takes place, all as a result of the severe jarrings of the neuronal tissues due to the repeated pommeling applied to the skull.[15]

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14. Brock.[7a]

15. Brock.[7a] Martland, H. S.: Punch Drunk, J. A. M. A. **91**:1103-1107 (Oct. 13) 1928. Siegal.[3a]

SUMMARY

The mental device of amnestic behavior, the psychological and psychopathological forces which precipitate it, the compensatory and defensive mechanisms engendered, the psychopathological memory dysfunction attending structural impairment, and the extent to which this behavior is reflective of constitutional, somatogenic, and social personality factors, are analyzed—this in order to formulate a comprehensive conception of the patient's mental and physical capacity responsible for his amnestic disorder. Psychogenic, nontraumatic, and traumatically induced amnesias are distinguished, a representative variety of physical and psychological patterns are accounted for; reasons for their appearance are given, and the respective qualitative and quantitative anatomical influences are indicated.

To recapitulate, amnestic states, as psychological nonorganic phenomena, are reactions or expressions of persons when under difficult and stressful circumstances. The symptoms may be reflective of psychological exposure to peril or of rejection from consciousness of objectionable memories, feelings, impulses, and ideas, or of threat to psychical or physical integrity.

When of nonorganic origin, the amnestic mechanisms are indicative of a significant correlation between the memory loss and the ominous situation which the patient is endeavoring to avoid by way of his display of absent memory—this in order to enable him to carry on within certain of his spheres of action and to retain at least some measure of capability and self-esteem.

The need for analysis and interpretation of this distress symbol cannot be overestimated when considered in its contextual relation to the plethora of psychoneurotic and psychosomatic disorders arising from disappointments, vacillation, tensions generated by opposing desires, unpleasant situations, and rumination over past conduct.

As to the malingering mechanism, to quote from the Russian psychiatrist Ossipov,[12b] "Every malingerer is really an unstable person . . . who by imitating a psychosis merely accentuates his own latent tendencies so that malingering is really pseudo malingering." The simulations, pretenses, causal factors, and differentiation of malingering from other psychical situations where memory is in issue are detailed.

When of organic origin, amnestic symptoms, qualitative and quantitative, traumatic and nontraumatic, reversible and irreversible, as set forth in this account, are the result of damage to the neuronal structures.

As therapeusis in disordered personality situations due to nonorganic phenomena or structural alterations is dependent upon precise knowledge of the etiology and character of the amnestic symptomatology, it is of critical importance that an accurate diagnosis be established in order to evaluate causality prior to a determination of the therapeutic regimen of choice.

On the basis of my extended personal observations carried out in hospital wards, and outpatient clinics, as well as upon noninstitutional patients, all investigated in their respective settings, the salient features of the divers patterns and relative extent of the amnesias are produced in some detail in this study. It is trusted that the essential nature of the differentials outlined in the various disorders of memory function will be of aid in arriving at diagnostic evaluations—prerequisites to therapeutic determination and prognostic outlook.

211 E. 35th St.

STUDIES ON EXCRETION OF TOTAL NEUTRAL 17-KETOSTEROIDS IN SCHIZOPHRENIC PATIENTS

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ALTHOUGH previous studies on the levels of serum sodium and serum potassium in schizophrenic patients yielded no abnormal results,[1] it was suspected that some defect might exist in the function of the pituitary-adrenal cortex complex which would be reflected in an altered excretion of the total neutral 17-ketosteroids. Differences of opinion exist among investigators as to this possibility. Parsons and associates [2] claimed that there is no disorder of pituitary-adrenocortical function in psychotic patients, as evidenced by the lymphocytopenia resulting from electric shock, insulin shock, and epinephrine. However, they did claim that psychological stresses revealed a disorder in the endocrine function, as indicated by the absence of lymphocytopenia. Hoagland and associates [3] also failed to produce lymphocytopenia in schizophrenic patients after exposure to stressful situations, such as cold and pursuit-meter operations. Hemphill and associates [4] observed that electric shock therapy and metrazol® (pentylenetetrazole) therapy caused an increase in the excretion of the 17-ketosteroids. Hoagland and associates [5] claimed

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1. Gottfried, S. P.: Blood Chemistry of Schizophrenic Patients Before, During and After Insulin Shock Therapy: Preliminary Studies, Arch. Neurol. & Psychiat. **62**:809 (Dec.) 1949.

2. Parsons, E. H.; Gildea, E. F.; Ronzoni, E., and Hulbert, S. E.: Comparative Lymphocytic and Biochemical Responses of Patients with Schizophrenia and Effective Disorders to Electroshock, Insulin Shock, and Epinephrine, Am. J. Psychiat. **105**:573, 1949.

3. Hoagland, H.; Elmadjean, F., and Pincus, G.: Stressful Psychomotor Performance and Adrenal Cortical Function as Indicated by the Lymphocytic Response, J. Clin. Endocrinol. **6**:301, 1946.

4. Hemphill, R. E.; MacLeod, L. D., and Reiss, M.: Changes in the Output of 17-Ketosteroids After Shock Treatment, Pre-Frontal Leucotomy, and Other Procedures, J. Ment. Sc. **88**:554, 1942.

5. Hoagland, H.; Malamud, W.; Kaufman, I. C., and Pincus, G.: Changes in the Electroencephalogram and in the Excretion of 17-Ketosteroids Accompanying Electroshock Therapy of Agitated Depression, Psychosom. Med. **8**:246, 1946.

that the 24-hour output of 17-ketosteroids was the same in normal as in schizophrenic subjects but that the normal person showed a pronounced diurnal rhythm of excretion, which the psychotic patient frequently lacked.

Because of the confusion in existing data, it was thought that further studies on the pituitary-adrenocortical activity of schizophrenic patients, as indicated by the urinary excretion of total neutral 17-ketosteroids, was warranted. These studies were to include analyses of 17-ketosteroids upon admission, after hospitalization without shock treatment, and during and after insulin or electric shock therapy.

METHODS EMPLOYED

Young male patients who had had an illness diagnosed as schizophrenia for less than four years were chosen for study. On the patient's being admitted to the hospital, either single or serial determinations of the 17-ketosteroid excretion were performed. As the patient underwent insulin or electric shock therapy, determinations were performed during and after treatment. For those patients who did not receive shock therapy an analysis was made after an interval of time had elapsed, especially if a remission in their condition had occurred. Included in this study were a few patients who had been hospitalized more than 10 years and were considered incurable.

Twenty-four-hour specimens of urine were collected for analysis, 8 cc. of concentrated hydrochloric acid being used as a preservative. During this period the patient either was confined or was restricted to occupational therapy. Creatinine coefficients were determined on each specimen, and only the urines giving a value above 20 were accepted for analysis. When analyses were performed on the patients undergoing insulin or electric shock treatment, urines were collected only on those days on which treatment was administered and a coma was recorded.

The procedure used was a modification of the method of Callow and associates,[6] the extraction with carbon tetrachloride being carried out twice and back extractions being performed on the reagent used in each washing. The residue was carried through a separation with Girard's T reagent, as described by Talbot and others,[7] and the colorimetric determination was performed by the Zimmerman reaction, as also described by Talbot and associates.[7] The amount of 17-ketosteroids was calculated from a calibration curve, dehydroisoandrosterone acetate being used as the standard, and checks were made on the color development by running a standard with each series of determinations. Each determination was carried out in duplicate. Recoveries were performed frequently, averaging 78%, and were never less than 76%.

RESULTS

In Table 1 are listed the 24-hour excretions of the total neutral 17-ketosteroids for normal subjects and for schizophrenic patients. The results for the normal subjects ranged from 2.2 to 12.0 mg. with a mean of 7.7 ± 2.3 mg. These results compare favorably with those obtained by Callow and associates,[6] who reported a range of 3.5 to 15.0 mg., with an average of 9.1 mg., and also with the results of Hemphill and associates,[4] who reported a range of 6.0 to 15.0 mg. Our results are somewhat lower than those reported by Talbot and associates, as cited by Escamilla [8] —8.8 to 15.6 mg., with an average of 11.0 mg.

The results obtained for the schizophrenic patients are also listed in Table 1. They are only slightly lower than the normal values, ranging from 1.0 to 13.3 mg.,

6. Callow, N. H.; Callow, R. K.; Emmens, C. W., and Stroud, S. W.: Methods of Extracting Compounds Related to Steroid Hormones from Human Urine, J. Clin. Endocrinol. **1**:76, 1939.

7. Talbot, N. B.; Butler, A. M., and MacLachlan, E.: The Colorimetric Assay of Total α and β 17-Ketosteroids in Extracts of Human Urine, J. Biol. Chem. **132**:595, 1940.

8. Escamilla, R. F.: Diagnostic Significance of Urinary Hormonal Assays: Report of Experience with Measurements of 17-Ketosteroids and Follicle Stimulating Hormones in the Urine, Ann. Int. Med. **30**:249, 1949.

with a mean of 6.7±2.8 mg. As far as the accuracy of the method is concerned, the results for the schizophrenic subjects are not significantly different from those for the normal subjects. It may be stated, therefore, that under conditions devoid of any apparent stress (under which conditions the samples of urine were collected) there appears to exist no difference between the activity of the adrenal cortex in the schizophrenic patient and that in the normal subject as determined by the output of 17-ketosteroids.

In several instances, serial determinations were performed on both normal and schizophrenic subjects, and in some of these a wide range of results were obtained, a few being low. But when the results were averaged, the mean always fell within

TABLE 1.—*Excretion of Total Neutral 17-Ketosteroids by Normal and by Schizophrenic Subjects*

	Total Neutral 17-Ketosteroids (Mg. Excreted per 24 Hr. as Dehydroisoandrosterone Acetate)
Normals	
1	4.9, 10.8, 6.0, 6.5 (average 7.1)
2	2.5, 9.3, 6.7, 9.9 (average 7.1)
3	10.7
4	10.1, 9.0, 7.6, 8.8 (average 8.9)
5	2.2, 9.4, 8.5, 12.0 (average 8.0)
6	9.3
7	5.1
8	4.2
Schizophrenic Subjects	
9	5.2, 5.0
10	3.6
11	1.4
12	5.2
13	1.5
14	1.0
15	7.4
16	8.7
17	6.3
18	3.1
19	7.3
20	5.3
21	10.9
22	2.8, 3.8, 11.2 (average 6.9)
23	10.4, 9.1, 8.4 (average 9.6)
24*	3.9, 4.9, 7.4 (average 5.4)
25*	3.5, 2.4, 7.3 (average 4.4)
26*	10.6, 8.1, 7.8, 7.8 (average 11.4)
27*	12.6, 6.7, 10.6 (average 10.0)
28	13.3
29	11.3
Normal mean	7.7±2.3
Schizophrenic mean	6.7±2.8

* These patients had been hospitalized over 10 years. The other patients were all newly admitted, and for none had the diagnosis been made more than four years ago.

normal limits. One patient with Addison's disease was studied as a control. The four determinations obtained on this patient varied from 1.85 to 2.43 mg., with a mean of 2.23 mg., which is below normal. Consequently, it is advocated that, for a more accurate evaluation, at least three or four determinations be performed on each patient, if it is desired to use the excretion of 17-ketosteroids as an index of adrenocortical activity.

Even though an excretion of less than 2 mg. was obtained for three of the schizophrenic patients studied, it is impossible to exclude the possibility that serial determinations on these patients might have yielded an average result within the normal range, as was the case with two of the normal subjects (2 and 5). Also, in these three patients no clinical sign of hypofunction of the adrenal cortex could be observed. For these reasons, it is difficult to ascribe the low values to pituitary-adrenocortical insufficiency, although the latter cannot be ruled out. Another com-

plicating factor is that the 17-ketosteroids are not an absolute measure of adrenocortical activity, but they also determine the androgens associated with testicular function. Consequently, the determination of blood and urinary corticosteroids would be a truer index of adrenocortical activity. This study is, at present, being undertaken in our laboratory.

In Table 2 are listed the excretion of the 17-ketosteroids in patients receiving insulin or electric shock therapy. All patients studied during treatment showed a decided increase in the excretion of the 17-ketosteroids. After treatment had been terminated, the values dropped somewhat, but all were considerably higher than the pretreatment levels. In two cases in which analyses were made after another 10 to 14 days had elapsed, the values dropped still further and tended to approach the pretreatment level.

From these results it must be postulated that insulin causes increased pituitary-adrenocortical activity, resulting in an elevated excretion of 17-ketosteroids. The

TABLE 2.—*Excretion of Total Neutral 17-Ketosteroids by Schizophrenic Patients Before, During, and After Insulin and Electric Shock Therapy*

			Total Neutral 17-Ketosteroids (Mg. Excreted in 24 Hours as Dehydroisoandrosterone Acetate)			
Patient	Treatment	Change in Condition	Before Treatment	During Treatment	Within 5 Days After Treatment Terminated	14 to 18 Days After Treatment Terminated
11	Insulin shock	Great improvement	1.4	....	13.9	....
12	Insulin shock	Great improvement	5.2	25.9	16.0	8.3
22	Insulin shock	Great improvement	5.8	14.8	14.4	12.3
10	Insulin shock	Moderate improvement	3.6	18.5	10.3	....
21	Electric shock	Great improvement	10.9	....	9.2	....
24	Electric shock	No improvement	13.3	....	12.5	....
19	Electric shock	Slight improvement	5.1	6.9	6.1	....
29	Electric shock	Slight improvement	11.3	7.7	12.3	....

mechanism of this reaction probably lies in the insulin stimulating the anterior lobe of the pituitary to increased secretion of adrenocorticotropin, which, by its action on the adrenal cortex, causes an increased secretion of the adrenocortical hormones to oppose the action of the insulin, thus resulting in an elevation in the urinary 17-ketosteroids. Unfortunately, it was not possible to study the steroid excretions in normal subjects under the influence of insulin. Therefore, it cannot be stated whether or not the results obtained are specific for the schizophrenic patient. Since all the insulin-treated patients in this study responded to treatment, it is not possible to establish any relationship between the excretion of urinary total neutral 17-ketosteroids and the condition of the schizophrenic patient after therapy had been terminated.

Of the four patients receiving electric shock therapy, not one had an elevated excretion of 17-ketosteroids, either during or after treatment, even though three of the patients showed signs of improvement. It therefore appears that electric shock therapy does not stimulate adrenocortical activity. However, for three of the patients the pretreatment 17-ketosteroids were above the mean upper normal limit of 10 mg. This might have some relation to the absence of an increase in the 17-ketosteroids during or after treatment.

In Table 3 are listed the urinary total neutral 17-ketosteroids in seven patients who did not receive shock therapy. Five of these patients were improved clinically to such an extent that they were permitted to go home on a trial visit. As soon as examination revealed improvement in their condition, 17-ketosteroid determinations were performed. In four of the five patients an increase of from 100 to 700% over the admission level was obtained, the values being higher than the mean upper normal value of 10 mg. In the fifth patient an increase was also obtained, but it was not significant. In the other two patients, in whom no improvement in the clinical condition was noted, no significant increase in the urinary total neutral 17-ketosteroids was obtained.

These results suggest that associated with improvement in the clinical condition of the schizophrenic patient is a sharp increase in the 17-ketosteroids, which may

TABLE 3.—*Comparison of Excretion of Total Neutral 17-Ketosteroids by Schizophrenic Patients upon Admission and During Subsequent Hospitalization, No Shock Therapy Being Administered*

	Total Neutral 17-Ketosteroids (Mg. Excreted in 24 Hours as Dehydroisoandrosterone Acetate)		
Patient	Upon Admission	During Hospitalization	Change in Clinical Condition
13	1.5	2 mo. later 10.2	Improvement
15	7.4	4 mo. later 16.0	Improvement
17	6.3	2½ mo. later 13.0	Improvement
18	3.1	3 mo. later 4.7	Improvement
20	5.3	2 mo. later 16.8	Improvement
19	7.3	5 mo. later 9.5	No improvement
9	5.2	1 mo. later 5.0	No improvement

reflect an increase in the pituitary-adrenocortical activity. Since it was not possible to study further the patients who had shown improvement and had been permitted to leave the institution, it is not possible to state whether and when the ketosteroids tended to drop.

However, it is not possible to reconcile these results with those obtained for the three patients who received electric shock therapy and showed improvement (Table 2), since none of these patients showed any elevation of the ketosteroids. Of course, in only one was there a pronounced improvement in the clinical condition similar to that obtained in the patients listed in Table 3. Another point to be considered is that for three of the four patients the pretreatment value was already higher than the mean upper normal limit. Consequently, it may be that an increased excretion of 17-ketosteroids in patients showing a remission in their condition can be obtained only when the pretreatment level is not elevated.

The results here presented must therefore be considered to be merely indicative. Further studies, more vigorously controlled and more extensive, in which the patient is followed for a longer period, are necessary before any conclusions can

be drawn as to the relation of pituitary-adrenocortical activity to schizophrenia. These studies are being carefully planned and will be carried out in the very near future.

SUMMARY

Urinary total neutral 17-ketosteroid determinations were performed on schizophrenic patients upon admission, during hospitalization, and during and after insulin or electric shock therapy.

The mean value for the schizophrenic patients upon admission agreed closely with that obtained for a series of normal persons. However, the range for the schizophrenic patients was wider than that for the normal subjects, and low results, indicative of a possible adrenocortical insufficiency, were obtained in several patients.

It is suggested that in performing 17-ketosteroid determinations as an index of adrenocortical activity, serial analyses always be run. A single determination may, for some reason, be abnormal, whereas the average for a series of determinations may lie within the normal range.

In patients receiving insulin shock treatment, an elevation in the urinary 17-ketosteroids was obtained. No increase was obtained in patients receiving electric shock treatment.

Four of five patients showing a remission without receiving shock treatment had an elevation in the urinary 17-ketosteroids of 100 to 700%. Two patients not showing a remission revealed no such elevation. This indicates that a surge in pituitary-adrenocortical activity may be associated with improvement in the condition of the schizophrenic patient.

TETANY AND EPILEPSY

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BEFORE the functions of the parathyroids and their role in the pathogenesis of parathyroid tetany were known, Mikulicz [1] (1886) and Hoffmann [2] (1888) had reported cases in which thyroidectomy was followed by typical attacks of epilepsy alternating with tetany. Kraepelin [3] (1890) also reported a case of postoperative epilepsy but did not mention symptoms of tetany. Many papers on the subject were published later, and at present over 100 cases are recorded in the literature. After it had been proved that parathyroid insufficiency was the cause of postoperative tetany, the problem of a possible relation between tetany and epilepsy arose in those cases in which both syndromes were present. Two sets of opinions were current. According to Sachs [4] (1926) and Kalischer [5] (1926), tetany and epilepsy are two separate diseases, which happen to occur simultaneously in the patient, without there being any causal relation between them. On the other hand, Westphal [6] (1901), Ehrhardt [7] (1902), and Pineles [8] (1905) believe that the association of the diseases is not mere coincidence, and Redlich [9] (1911) definitely maintained that tetany is the causative factor of epilepsy in such cases. All arguments in favor of one hypothesis or the other were at first based exclusively on clinical observations, but since the discovery that the electroencephalogram shows more or less typical alterations in cases of epilepsy it can be used to throw light on these cases.

Electroencephalograms in cases of tetany with or without epilepsy have been published (Kowallis,[10] Odoriz and associates,[11] Sutphin and associates,[12] Tauben-

1. Mikulicz, J.: Beitrag zur Operation des Kropfes, Wien. med. Wchnschr. **1**:40, 1886.
2. Hoffmann, J.: Zur Lehre von der Tetanie, Deutsche Arch. klin. Med. **43**:53, 1888.
3. Kraepelin, E.: Zur Myxödemfrage, Neurol. Centralbl. **9**:65, 1890.
4. Sachs, I.: Besteht ein Zusammenhang zwischen Epilepsie und Tetanie? Deutsche Ztschr. Nervenh. **92**:304, 1926.
5. Kalischer, S.: Die Beziehungen der Tetanie zur Epilepsie, Arch. Psychiat. **78**:168, 1926.
6. Westphal, A.: Weiterer Beitrag zur Lehre von der Tetanie, Berl. klin. Wchnschr. **33**: 849, 1901.
7. Ehrhardt, O.: Über epileptiformes Auftreten der Tetaniathyreopriva, Mitt. Grenzgeb. Med. u. Chir. **2**:225, 1902.
8. Pineles, F.: Zur Pathogenese der Tetanie, Deutsche Arch. klin. Med. **85**:491, 1905.
9. Redlich, E.: Tetanie und Epilepsie, Monatsschr. Psychiat. u. Neurol. **30**:439, 1911.
10. Kowallis, G. F.: Spontaneous Parathyroid Insufficiency, Proc. Staff Meet., Mayo Clin. **16**:129, 1941.
11. Odoriz, J. B.; del Castillo, E. B.; Manfredi, F. J., and de la Balze, F. A.: El electroencefalograma en la insuficiencia paratiroidea humana, Medicina, Buenos Aires **4**:1, 1943.
12. Sutphin, A.; Albright, F., and McCune, D. J.: Five Cases (Three in Siblings) of Idiopathic Hypoparathyroidism Associated with Moniliasis, J. Clin. Endocrinol. **3**:625, 1943.

haus and Engle [13]), but so far no systematic work utilizing encephalography has been done in order to solve the problem of the relation of tetany and epilepsy. In collaboration with Odoriz (1948), I [14] have published the results of an electroencephalographic study of 14 cases of tetany; here, I shall report the findings in 6 cases of tetany—4 of the postoperative and 2 the idiopathic type—in which typical symptoms of epilepsy occurred. The diagnosis of parathyroid insufficiency was based on the clinical history of tetany, peripheral neuromuscular hyperexcitability, and hypocalcemia.

PROCEDURE

The following procedure was carried out whenever it was possible: The patients were observed for two weeks, and no treatment was given which might increase the blood calcium level. After this preliminary period, the fasting calcium and inorganic phosphate levels and the total protein concentration of the blood were determined. The electroencephalogram was recorded immediately after the blood sample was obtained, first with the patient breathing normally and then during voluntary hyperpnea. Pulmonary hyperventilation, as is well known, sensitizes the cortex and may bring out abnormalities in the electroencephalogram which would otherwise remain unnoticed. A dose of 1 gm. of calcium in solution was then injected intravenously, and the electroencephalogram was again recorded. The patient was then treated with vitamin D_3, or calciferol, given by mouth or, less frequently, intramuscularly, in doses of 10 to 15 mg. daily (400,000 to 600,000 I.U.), and approximately 15 gm. of calcium lactate was also given daily by mouth. The result of this treatment was controlled by means of weekly determinations of the blood calcium, which usually returned to normal after 20 days to 2 months. When the blood calcium was again at a normal level, clinical symptoms of parathyroid insufficiency usually had disappeared, and the electroencephalogram was again recorded.

A Grass oscillograph was used, with triple recordings in ink, at 25 mm. a second. Amplification was such that 50 μv caused a deflection of 7 mm. from the base line. The electrodes were placed on lines B and C (Gibbs) indiscriminately on the right or the left side of the head. A push-pull and two earth leads, one from each ear, were used in all cases. Bipolar leads were employed, but in some instances a monopolar lead was also used. The total blood calcium was determined by Marenzi and Gerschman's [15] method, and the inorganic phosphate, by Moore and Van Slyke's,[16] calcium ion was calculated from the total calcium, and protein concentration, by means of McLean and Hastings' nomogram.[17]

REPORT OF CASES

CASE 1.—The patient's father had died of dementia paralytica. At the age of 22, during her second pregnancy, she began to have pains in her limbs, after which vertigo, typical attacks of tetany, and epileptic fits appeared. The epileptic seizures were not preceded by aura and consisted of loss of consciousness, falling, convulsions, biting of the tongue, and frothing at the mouth, followed by amnesia. They occurred at irregular intervals, sometimes twice a week. When she was 25, the diagnosis of bilateral cataract was made, and 10 years later the cataracts were operated on successfully. At the age of 30 she had a grafting of parathyroid tissue, without improvement. At the age of 38 she suffered from maniacal attacks, lasting several hours. When she consulted me (1944) at the age of 43, a sensation of dizziness and vertigo were the most prominent disturbances.

13. Taubenhaus, M., and Engle, H. M.: Clinical Observations on a Case of Idiopathic Tetany and Epilepsy, J. Clin. Endocrinol. **5**:147, 1945.

14. Gotta, H., and Odoriz, J. B.: The Electroencephalogram in Hypoparathyroidism, Tetany and Epilepsy, J. Clin. Endocrinol. **8**:674, 1948.

15. Marenzi, A. D., and Gerschman, H.: Estudio comparativo de algunos métodos de determinación de la calcemia, Rev. Soc. argent. de Biol. **9**:375, 1933.

16. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

17. Prof. J. B. Odoriz interpreted the electroencephalograms, and Dr. F. Villalonga made the blood analyses.

May 2: The total blood calcium was 6.4 mg., and the inorganic phosphate 6.78 mg., per 100 cc. A rapid rhythm of 26 to 30 cps was recorded from the entire cortex. Hyperpnea produced the appearance of a few slow (6 cps) waves in series of three or four. Calciferol, 5 mg. (200,000 I.U.), was given daily by mouth. Two weeks later the clinical symptoms had disappeared; the blood calcium had risen to 10 mg. per 100 cc., and the blood phosphate had fallen to 4.86 mg. per 100 cc. The electroencephalogram was similar to that recorded before treatment, and again hyperpnea produced the appearance of slow waves. The patient has continued calciferol treatment for more than five years, and neither tetany nor epileptic fits have reappeared.

In summary, this case is one of idiopathic parathyroid insufficiency complicated by generalized motor epilepsy, without significant changes in the electroencephalogram. Calciferol treatment raised the blood calcium to a normal level and suppressed tetany, vertigo, and epileptic seizures.

Case 2.—The patient, when 17 years old, began to feel numbness in the fingers. Later he had two epileptic fits, at an interval of one year, each starting with a cry occurring at night. A third fit was produced by voluntary hyperpnea, induced by Dr. Munist, who referred the patient to me. This attack consisted of loss of consciousness, falling, and generalized tonic convulsions. The symptoms disappeared immediately after an intravenous injection of calcium gluconate. The blood calcium measured 6.5 mg., and the blood phosphate 7 mg., per 100 cc. When the patient came under my care, at the age of 21, he presented the peculiar changes in the tongue and nails described by Sutphin and his associates,[12] the development of which appears to be related to tetany. Trichophyton sp. developed in cultures of material obtained from the nails, and Candida sp., in material from the tongue. There was also incipient cataract in both eyes.

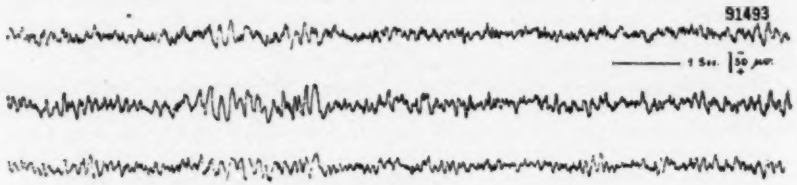

Fig. 1.—Electroencephalogram in Case 3.

On July 11, 1944, the blood calcium measured 8.5 mg., and the blood phosphorus 6.08 mg., per 100 cc. The electroencephalogram was normal, with an alpha rhythm of 10 cps. Hyperpnea did not produce significant changes. An electroencephalogram taken later showed the same characteristics. Calciferol treatment was begun, but the patient did not collaborate, and I lost sight of him.

In summary, the case is one of idiopathic parathyroid insufficiency complicated by epilepsy in which the electroencephalogram showed no significant abnormalities.

Case 3.—A woman aged 23 had thyroidectomy for diffuse toxic (exophthalmic) goiter on April 23, 1946, and tetany appeared on the day after the operation. Two weeks later she suddenly lost consciousness; there were conjugated upward movements of the eye and propulsion of the tongue to the left, causing it to be bitten and to bleed. Later, similar atacks occurred at night while the patient was asleep. A brother of the patient had convulsive seizures, followed by amnesia.

On May 21, the total blood calcium was 6.2 mg. per 100 cc. The electroencephalogram showed an abnormal slow rhythm of 4.5 to 8 cps, with an amplitude of 100 μv, appearing in groups of two to three waves, beginning in the frontal area and spreading backward to the occipital area. Hyperpnea produced the appearance of slow waves (2.5 cps; 80 μv). Injections of calcium did not modify the electroencephalogram. Treatment with calciferol (4 mg. daily) was prescribed, but the patient did not follow this schedule strictly. Ten months later she was again examined, having had five epileptic seizures in that time; the blood calcium was 8.8 mg. per 100 cc., and the electroencephalogram showed the same abnormalities as in the first record.

In summary, the case is one of postoperative tetany, with epileptic seizures beginning two weeks after the operation. The electroencephalogram showed cerebral dysrhythmia, which

was not modified by calcium injections and which was still present (as well as the epileptic fits) 10 months later. The blood calcium, however, was at almost a normal level (8.8 mg. per 100 cc.), as a result of calciferol treatment.

CASE 4.—The patient had had thyroidectomy for colloid goiter on April 24, 1939. Symptoms of tetany appeared the same day and recurred up to 1943, when she became pregnant. During her pregnancy, tetany was in remission, but reappeared after delivery. In March, 1944, she suddenly lost consciousness, fell, had generalized clonic convulsions and bladder incontinence, and frothed at the mouth. This condition lasted approximately 15 minutes and was followed by amnesia. Two weeks later she had a similar fit, after which she consulted me, being then 37 years old. On April 19, 1944, the blood calcium measured 6.6 mg., and the blood phosphate 6.8 mg., per 100 cc. The electroencephalogram showed a basic fast rhythm, interrupted by paroxysms of abnormal waves (5 cps, 120 μv), lasting up to 4 seconds. Among these waves were a few spikes up to 140 μv. This abnormal rhythm appeared almost simultaneously in the frontal, parietal, and occipital leads and was similar to that recorded in petit mal. While the electroencephalogram was being recorded, the patient had muscular cramps, i. e., symptoms of tetany, but no clinical signs which could be referred to the paroxysms. These abnormal rhythms should be considered as subclinical epileptic fits revealed by the electroencephalogram. The patient was placed under calciferol treatment (10 mg., or 400,000 I.U. given daily by mouth), and five weeks later she was again examined. The blood calcium measured 8.8 mg. per 100 cc. The electroencephalogram showed the same basic rhythm, but there were no paroxysms, and hyperpnea did not produce them. The patient was examined six times in the course of two years. On June 1, 1944, the blood calcium was 10 mg. per 100 cc., and the blood phosphate,

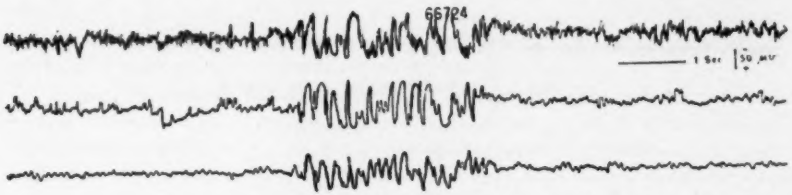

Fig. 2.—Electroencephalogram in Case 4.

5.8 mg. per 100 cc. The electroencephalogram was similar to the previous record, but there were no abnormalities, even during hyperpnea.

Calciferol treatment was then discontinued. One month later the blood calcium was down to 7.4 mg. per 100 cc. and the blood phosphate up to 6.7 mg. per 100 cc. There were no abnormalities in the first part of the record, but after injection of calcium a typical paroxysmal discharge appeared during hyperpnea. Other records were similar. The patient has been under observation for five years, during which time she has had no epileptic seizures, but symptoms of tetany are still present. The blood calcium is persistently low, and calciferol no longer raises it.

In summary, the case is one of postoperative tetany complicated by generalized motor epilepsy. The electroencephalogram showed paroxysms of abnormal waves, i. e., paroxysmal cerebral dysrhythmia.

CASE 5.—The patient had had thyroidectomy for cystic goiter on Aug. 12, 1941. A few days after the operation symptoms of tetany appeared. Three months later she suffered an attack of generalized tonic convulsions with loss of consciousness; she fell, bit her tongue, and had urinary incontinence. The fit lasted 10 minutes and was followed by amnesia. Later, epileptic seizures alternated with tetany. When I first saw her, in 1944, she was 40 years old. On Aug. 1, 1944, the blood calcium was 6.2 mg., and the blood phosphate 3.7 mg., per 100 cc. The electroencephalogram showed a fast rhythm (20 to 25 cps) with occasional single spikes and slow waves (6 to 7 cps), especially in records from the frontal leads. Hyperpnea did not modify the electroencephalogram but was followed by a severe attack of generalized tetany, similar to those appearing spontaneously. The electroencephalogram during this attack did not show any change revealing disturbances in purely cortical activity—only widespread typical

muscle potentials appeared. The frontal and parietal leads gave records which are more characteristic of electromyograms than electroencephalograms. Intravenous injection of calcium suppressed the muscular contractions of tetany, and muscle potentials disappeared in the electroencephalogram, which now showed the same features as before the attack of tetany. The patient was placed under calciferol treatment, after which the blood calcium was normal and there was hypercalcemia (12.5 mg. per 100 cc.). The electroencephalogram remained constant despite the changes in the blood calcium level. During the more than five years since the initiation of treatment the patient has had no more epileptic fits.

In summary, in this case postoperative parathyroid insufficiency was complicated by epileptic fits, but without abnormalities in the electroencephalogram. Records taken during tetany produced by hyperpnea, i. e., induced by alkalosis, showed no changes due to cortical disturbances but were disfigured by muscle potentials.

CASE 6 (courtesy of Dr. E. B. del Castillo).—A woman aged 23 had had thyroidectomy for goiter at the age of 19. Three days after the operation tetany appeared, and two months later she began to have epileptic fits, which recurred at irregular intervals sometimes as frequently as four times in two weeks. The patient referred to a sensation of "going away" preceding the

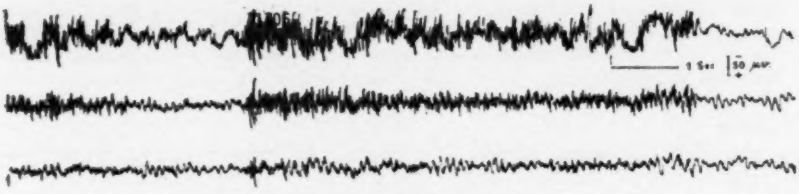

Fig. 3.—Electroencephalogram in Case 5.

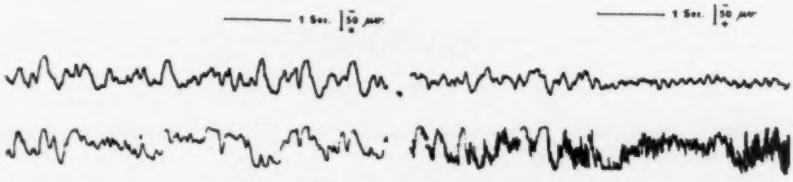

Fig. 4.—Electroencephalogram in Case 6.

fits; and, according to her relatives, she would press her stomach, groan, lose consciousness, fall down, have rigid convulsions, and bite her tongue. In November, 1940, parathyroid tissue was grafted, without benefit. The blood calcium was found to be low on several occasions (July 23, 1938, 5.5 mg.; Sept. 28, 1938, 5.4 mg.; Oct. 3, 1938, 5.0 mg.; June 28, 1939, 6.4 mg., and July 29, 1940, 6.5 mg., per 100 cc.). The electroencephalogram, recorded on Oct. 9, 1941, showed an undoubted abnormal rhythm, made up of slow waves (3 cps, 80 μv), more prominent in the occipital than in other leads. Hyperventilation increased the number of slow waves and increased their amplitude to 100 μv. An attack of tetany was also produced, and typical muscular potentials appeared in the record.

In summary, this case was one of parathyroid insufficiency complicated by epilepsy, with permanent dysrhythmia in the electroencephalogram. Hyperpnea increased the dysrhythmia and produced tetany, the electroencephalogram showing at the same time the abnormal rhythm of cortical disturbances due to epilepsy and the muscular potentials of tetany.

COMMENT

The observations of Odoriz and myself confirm the well-known fact that epilepsy may occur in the course of idiopathic or postoperative tetany. As far as

I know, no statistics have been published on the incidence of epilepsy in cases of tetany. Our own series comprises 25 patients with tetany, in 11 of whom the symptoms appeared shortly after thyroidectomy and disappeared spontaneously after a few days or weeks. None of these had epileptic fits. The other 14 had chronic tetany—3, idiopathic, and 11, postoperative. Five of these patients suffered from seizures, which were undoubtedly epileptic; a sixth patient had less typical signs of epilepsy. Therefore, in this series epilepsy occurred in at least one-third of the patients with chronic tetany. Two cases, certainly, perhaps also the third case, of chronic idiopathic tetany in this series were complicated by epilepsy, whereas this complication occurred in only 3 of the 11 cases of postoperative chronic tetany. The small number of cases does not permit further statistical analysis.

Symptoms of tetany always occurred before those of epilepsy. This was especially evident in postoperative tetany, in which the symptoms appeared suddenly; it was less so in idiopathic tetany, in which parathyroid insufficiency began more insidiously. In those cases in which it was possible to establish the facts, tetany had been present from 15 days to 5 years before epilepsy appeared. In other cases reported in the literature epilepsy occurred two days (Kraepelin [3]), six days (Geert-Jørgensen [18]), and nine days (Hoffmann [2]) after thyroidectomy. Barr and his associates [19] reported a case of epilepsy occurring 10 years after the operation, and von Fernbach and Szandanyi [20] referred to a case described by Hoesch in which epilepsy occurred 18 years after operation.

Usually the seizures had the characteristics of generalized motor epilepsy. One patient had epileptic fits alternating with attacks of vertigo, which were interpreted as epileptic "equivalents." Frequency of seizures varied considerably from one patient to another; some had fits twice a week; others had only two fits in the whole course of their illness.

Attacks of tetany alternated with epileptic seizures in some cases; in others parathyroid insufficiency was not manifest, but latent, and these had been mistakenly considered as cases of essential epilepsy, until the fortuitous provocation of Trousseau's sign, (carpospasm) while the blood pressure was being taken, the appearance of cataract, or some other sign of tetany gave a clue to the right diagnosis.

The electroencephalogram, even after hyperpnea, revealed no abnormality in three of the cases, except for a few isolated slow waves or spikes, insufficient in themselves to constitute definite dysrhythmia. It is, of course, possible that, although the electroencephalogram was normal at the time the records were taken, the patients may have had abnormal rhythms at other times.

The electroencephalograms in the other three cases were definitely abnormal. In Case 4 the record showed paroxysms of slow waves and spikes, although there were no concomitant clinical signs, thus presenting a "subclinical" form of epilepsy.

18. Geert-Jørgensen, E.: Deux cas de tétanie parathyroïdoprive combinée à l'épilepsie, Acta psychiat. et neurol. **7**:159, 1932.

19. Barr, D.; MacBryde, C. M., and Sanders, T. E.: Tetany with Increased Intracranial Pressure and Papilledema, Tr. A. Am. Physicians **53**:227, 1938.

20. von Fernbach, J., and Szandanyi, Z.: Mit Hilfe des Elektrokardiogrammes diagnostizierte tetanoide Epilepsie, Klin. Wchnschr. **19**:372, 1940.

The electroencephalogram recorded five and six weeks later, when the blood calcium had returned to normal, as a result of treatment with calciferol, showed no paroxysms, and even hyperpnea did not produce them. Paroxysm reappeared in the electroencephalogram one month after treatment had been discontinued and the blood calcium was again at a low level. In Case 3 the record showed intermittent dysrhythmia, persisting for months, although treatment had raised the blood calcium to an almost normal level (8.8 mg. per 100 cc.). In Case 6 there was permanent dysrhythmia, which became more pronounced after hyperpnea.

The association of tetany and epilepsy cannot be dismissed as mere coincidence. Three clinical facts indicate that parathyroid insufficiency is a causal factor in epileptic seizures: (*a*) The incidence of epilepsy is high in cases of chronic tetany (one-third of our patients); (*b*) tetany always precedes the appearance of epileptic seizures in cases of tetany associated with epilepsy; (*c*) epileptic fits disappear when tetany is controlled by adequate treatment (Holtz,[21] Beretervide and associates,[22] Elliot,[23] Knospe,[24] Eaton and Haines,[25] Himsworth and Maizels,[26] Gotta and Odoriz,[14] and the cases reported here).

The electroencephalogram demonstrates this even more clearly than simple clinical observation. Thus, in Case 4, in which the electroencephalogram showed paroxysms of slow waves and spikes, constituting a "subclinical" form of epilepsy, the record was normal after the blood calcium had been raised by treatment with calciferol, and again showed paroxysms when the blood calcium fell, because of the treatment having been discontinued. Calciferol does not cure parathyroid insufficiency; it only raises the blood calcium, thus suppressing the symptoms of tetany; the underlying physiological disturbance remains unchanged. Hypocalcemia acts, therefore, as a precipitating factor, inducing epilepsy in these cases.

The mechanism by which hypocalcemia produces epilepsy is still unknown. Probably there is a disturbance in the physicochemical structure of the brain cells, which must take some time to develop, for acute transitory tetany is not complicated by epilepsy; only in cases of chronic tetany is there a significant association of the two syndromes. The disturbance is not localized in certain cerebral foci but extends throughout the cortex, as is shown in the electroencephalogram.

Hypocalcemia *per se* cannot produce epilepsy. The majority of cases of tetany are not complicated by epilepsy, and there was no significant correlation between the blood calcium level and the degree of abnormality in the electroencephalogram in our series, either in the same patient or when different patients were compared. Hypocalcemia produces epilepsy when it occurs with other unknown, probably constitutional, factors. This opinion is also that of Holtz,[21] Grinker,[27] Taubenhaus and Engle [13] and others.

21. Holtz, F.: Bericht über Erfahrungen mit A. T. 10, Klin. Wchnschr. **13**:104, 1934.

22. Beretervide, J. J.; Cárrega Casaffousth, C. F., and Rosenblatt, S.: Un caso de tetania-epilepsia paratiropriva, Prensa méd. argent. **22**:2293, 1935.

23. Elliot, T. R.: Treatment of Tetany, Lancet **1**:641, 1935.

24. Knospe, H.: Über tetanische Störungen, Deutsche med. Wchnschr. **65**:752, 1939.

25. Eaton, L. M., and Haines, S. F.: Parathyroid Insufficiency with Symmetrical Cerebral Calcification, J. A. M. A. **113**:749 (Aug. 26) 1939.

26. Himsworth, H. P., and Maizels, M.: Vitamins D_2 and D_3 and A. T. 10 in Congenital Thyroid and Parathyroid Deficiency, Lancet **1**:959, 1940.

27. Grinker, R.: Neurology, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1937, p. 844.

The electroencephalogram also shows the essential difference between the mechanism of an epileptic seizure and that which produces an attack of tetany. In the former there is a disturbance in the electrical activity of the cortical brain cells; in the latter the electroencephalogram shows potentials originating in the muscles superimposed on the record of cerebral activity.

Epilepsy and tetany are separate entities, although in some cases it is difficult to determine which of the two is the cause of the clinical symptoms. Moreover, it is possible that the symptoms are of mixed origin. Thus, hyperventilation increases the severity of tetanic and epileptic symptoms. In one of our cases (Case 6) hyperpnea produced an attack of tetany, and at the same time the already existing cerebral dysrhythmia was increased. The difficulty in establishing a diagnosis does not, however, justify the hybrid term "tetany-epilepsy," used by some authors, because the name suggests a definite nosological entity, which does not exist. In certain cases tetany is complicated by epilepsy, because in these cases persistent hypocalcemia, acting on a suitable underlying constitution, is a precipitating factor of epileptic seizures.

CONCLUSIONS

Tetany and epilepsy are separate entities. When they occur simultaneously in a patient, epilepsy follows tetany. In subjects with an epileptic constitution hypocalcemia acts as a precipitating factor of epileptic seizures. Abnormalities observed in the electroencephalogram of these patients appear in all the leads (frontal, parietal, and occipital); they extend, therefore, throughout the cortex and are in no way different from disturbances observed in other cases of epilepsy. In all cases of epilepsy of unknown origin the possibility of parathyroid insufficiency should be considered; symptoms of tetany should be looked for, and the concentration of blood calcium and inorganic phosphate should be determined. In these cases treatment with barbiturates gives no results. The proper procedure consists in the elevation of the blood calcium level by means of calciferol or dihydrotachysterol (Holtz's A. T. 10), which gives excellent results if administered in adequate doses for a sufficiently long time. Treatment directed toward increasing the blood calcium is specific for parathyroid insufficiency to such a degree that when it causes the disappearance of epileptic fits it may be safely affirmed that hypocalcemia due to hypoparathyroidism acted as a precipitating factor in the seizures.

Av. Quintana 116.

PAPILLEDEMA IN POLIOMYELITIS

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AND
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DURING 1949 and 1950, 106 patients with acute anterior poliomyelitis were treated on the neurological service of the New York Hospital. During early convalescence changes in the optic fundi resembling papilledema developed in five of these patients. This finding was remarkable, since abnormalities in the optic fundi are apparently rare in poliomyelitis and have been noted by only a few of those who have written about the illness.

Wickmann,[1] in his monograph on poliomyelitis, published in 1907, reported one patient with "papillitis." Ruhräh and Mayer,[2] in 1916, reported that 2 out of 338 patients with poliomyelitis had associated disease of the optic nerves. In neither of these patients was examination of the optic fundi reported. Hall,[3] in 1918, described a case of poliomyelitis in which 5.5 D. of neuroretinitis appeared on the 20th day of the illness. These changes were associated with elevation of the spinal fluid pressure, and recovery was complete 10 weeks after the appearance of the papilledema. Ghormley,[4] in 1925, reported a case in which the patient complained of blurred vision four weeks after the onset of acute poliomyelitis, and examination of the optic fundi showed moderately swollen nerve heads and dilated veins. The peripheral visual fields were slightly constricted. Observations on the central visual fields and cerebrospinal fluid pressure were not reported. Ghormley found no abnormalities of the optic fundi in 155 subsequent cases of poliomyelitis. Ayer and Trevett,[5] in 1934, reported in detail a case of anterior poliomyelitis in which the patient complained of headache during the fifth week of his illness. He was found to have papilledema of 2 D. and small retinal hemorrhages in one fundus. Vision

From the Department of Medicine (Neurology), Cornell University Medical College and the New York Hospital.

1. Wickmann, I.: Über die Prognose der akuten Poliomyelitis und ätiologisch verwandter Erkrankungen, Ztschr. klin. Med. **63**:362, 1907.

2. Ruhräh, J., and Mayer, E. E.: Poliomyelitis in All Its Aspects, New York, Lea & Febiger, 1917.

3. Hall, G. W.: Report of a Case of Poliomyelitis of the Bulbo-Spinal Type Presenting Rather Unusual Eye Symptoms, J. Nerv. & Ment. Dis. **48**:445, 1918.

4. Ghormley, R. K.: Optic Neuritis in Infantile Paralysis, J. A. M. A. **84**:570 (Feb. 21) 1925.

5. Ayer, J. B., and Trevett, L. D.: Acute Poliomyelitis with Choked Discs: Notes on Prolonged Observation of the Spinal Fluid and the Use of the Respirator, Arch. Neurol. & Psychiat. **31**:396 (Feb.) 1934.

was stated as being entirely normal. Lumbar puncture revealed a pressure of 700 mm. of spinal fluid with pleocytosis. Blurred disks persisted for two months after they were initially observed. In 1947 Voisin and Bonduelle [6] reported a case of acute anterior poliomyelitis. Six weeks after the onset of the illness the patient complained of headache and stiff neck. Examination of the optic fundi showed elevation of the optic disks, suggesting papilledema. Eight days later the spinal fluid pressure was 210 mm. of fluid, and one month later the elevation of the optic disks had disappeared.

REPORT OF CASES

CASE 1.—G. H., a white man aged 22, who had contracted acute poliomyelitis six weeks previously, was admitted to the New York Hospital on Sept. 23, 1949. He had been in a respirator continuously since two days after the onset of his illness, and at another hospital he was found to have papilledema and small hemorrhages about the margins of both disks, four weeks after the onset of his illness. On admission to the New York Hospital, he had severe flaccid paralysis of all extremities and was unable to breathe without a respirator. His blood pressure was 210/115 mm. Hg, and the optic fundi revealed papilloretinal edema of 2 D. with arterial narrowing and flame-shaped hemorrhages. The patient's only visual complaint was diplopia. The visual fields were grossly normal, and visual acuity was unaltered. Spinal fluid studies were not done because it was impossible to remove the patient from the respirator long enough to carry out lumbar puncture. Over a period of eight weeks after admission, though he showed little other improvement, his papilledema and retinal hemorrhages disappeared, and his blood pressure fell to 160/100. The optic fundi and visual function have remained normal since.

CASE 2.—R. C., a white man aged 20, was admitted on Jan. 5, 1950, with acute anterior poliomyelitis. There developed flaccid paralysis of all four extremities, but he had no signs of involvement of the cranial nerves or reduction in vital capacity. He gave a history of having double vision with the onset of his poliomyelitis, as he had had with all febrile illnesses in the past. The optic fundi were normal on his admission, and the spinal fluid was under normal pressure and contained 105 white cells per cubic millimeter and 69 mg. of protein per 100 cc. Fifty-one days after admission he complained of a recurrence of double vision, and at this time 2 D. of papilledema was noted bilaterally along with distention of the retinal veins, the fundi having appeared normal one week previously. He had no defect in extraocular movements; visual acuity was unaltered, and the central and peripheral visual fields were normal. The spinal fluid pressure at this time was 180 mm. of fluid; there were no cells, and the protein measured 147 mg. per 100 cc. An electroencephalogram and x-ray picture of the skull were normal. Over the next 30 days, his optic fundi returned to normal, he had no further visual complaints, and his spinal fluid pressure dropped to 80 mm. of fluid. The optic fundi have remained normal since.

CASE 3.—S. S., a white girl aged 18, was admitted on Sept. 17, 1950. During the first week of her illness there developed marked weakness of both lower extremities and of the abdominal muscles and moderate weakness of both upper extremities. She showed no signs of cranial nerve involvement, and at the time of admission the optic fundi appeared normal. The vital capacity remained adequate throughout her illness. Thirteen days after the onset of her illness, and seven days after her admission to the hospital, she complained of headache, nausea, diplopia, and photophobia. Examination revealed no defect in extraocular movements, but the optic fundi showed 3 D. of papilledema, with distended veins. Visual acuity was normal, and the visual fields were grossly normal. The spinal fluid pressure at this time was 390 mm. of fluid, and the protein content was 162 mg. per 100 cc. Twelve days after the appearance of the papilledema the optic fundi had returned to normal.

CASE 4.—J. F., a white man aged 20, was admitted on Sept. 28, 1950, with an illness of three days' duration. At the time of admission he was found to have flaccid quadriplegia and respiratory insufficiency. His blood pressure was 160/90, and the optic fundi showed no

6. Voisin, J., and Bonduelle, M.: Syndrome méningé à rechute avec stase papillaire importante au cours d'une poliomyélite antérieure aiguë, Rev. neurol. **79**:39, 1947.

abnormality. He was placed in a respirator immediately after admission. One week later he complained of blurred vision; examination of the fundi at this time showed 3 D. of papilledema, with dilated veins but no hemorrhages. There was no edema of the face or scalp.

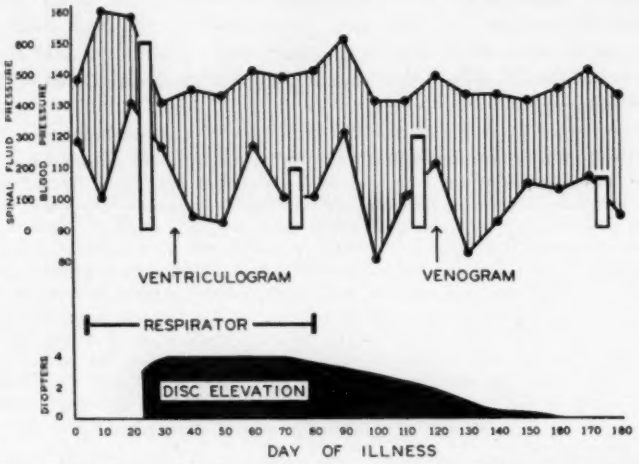

Fig. 1.—Clinical course of H. H., who exhibited papilledema during the convalescent stage of anterior poliomyelitis.

Fig. 2.—Ventriculogram of H. H. obtained while papilledema was present.

Spinal fluid on admission revealed a pressure of 140 mm. of fluid, 325 cells per cubic millimeter and 99 mg. of protein per 100 cc. Lumbar puncture could not be performed when the papilledema was most prominent because of the need for the respirator. The visual

fields were grossly normal, and acuity was unimpaired. The electroencephalogram showed no abnormality. Two and one-half weeks after the onset of papilledema the fundi were normal and have remained so.

CASE 5.—Figure 1 is a graphic presentation of the clinical course of H. H., a white man aged 28, who was admitted on Aug. 16, 1950, with paralysis of the lower extremities and slight respiratory insufficiency. Within 24 hours he had quadriplegia and had to be placed in a respirator. His blood pressure at this time was 138/118, and the optic fundi were not remarkable. Blurred vision and diplopia were noted by the patient three weeks later. Examination of the optic fundi showed papilledema of 4 D. bilaterally. Spinal puncture revealed an initial pressure of 600 mm. of spinal fluid, with 47 lymphocytes per cubic millimeter and 306 mg. of protein per 100 cc. The elevation of the optic disks gradually decreased, and disappeared 140 days after it was first observed. It is important to note, and can clearly be seen in Figure 1, that the hypertension outlasted the papilledema and that the latter persisted beyond

Fig. 3.—Dural-sinus venogram of H. H., obtained while 3 D. of papilledema was present.

the period that artificial respiration was necessary. Ventriculography (Fig. 2) and dural-sinus venography (Fig. 3), performed on this patient,[7] revealed no evidence of ventricular dilatation or displacement, and there was no obstruction of the venous sinuses or evidence of collateral circulation. The electroencephalogram contained an excess of 6-per-second activity in the occipital region. The visual acuity was normal, and the visual fields were grossly normal.

In summary (Table 1), five patients recovering from poliomyelitis with moderate to severe quadriplegia were found to have papilledema during the early stage of convalescence from the illness. Papilledema was first observed 11 to 48 days after the acute onset of the illness and persisted from 13 to 140 days, with an average duration of 60 days. Common complaints leading to this observation were diplopia and blurred vision associated with the diplopia. Three of the five patients had

7. Dr. Bronson S. Ray and Dr. Howard Dunbar carried out these procedures.

systemic arterial hypertension; the same three patients required a respirator, and in two of these the papilledema outlasted the need for the respirator. The spinal fluid pressure was elevated in the three cases in which measurement was possible.

Each of the five patients had acute poliomyelitis. The clinical course of the illness in each case was marked by headache, fever lasting 5 to 10 days or more, and the development of muscular paralysis with a typical anterior horn cell distribution. No patient exhibited any defects in sensation, and pleocytosis was found at the time of onset of the illness in the four patients who had lumbar punctures. Painful, stiff

TABLE 1.—*Clinical Findings in Five Cases in Which Papilledema Developed During Convalescence from Anterior Poliomyelitis*

Patient	Paralysis	Visual Complaint	Elevated Optic Disk: First Noted	Elevated Optic Disk: Gone	Respirator	Blood Pressure	Spinal Fluid: Pressure, Mm.	Spinal Fluid: Cells, Cu. Mm.	Spinal Fluid: Protein, Mg./100 Cc.
G. H. (Case 1)	Four extremities and trunk	Diplopia	Day 29	Day 81 Duration: 52 days	Yes	180-240 / 95-120	...	..	...
R. C. (Case 2)	Four extremities and trunk	Diplopia	Day 48	Day 76 Duration: 28 days	No	110-130 / 75-85	180	0	147
S. S. (Case 3)	Four extremities and trunk	Photophobia and diplopia	Day 13	Day 26 Duration: 13 days	No	105-125 / 65-85	390	11	162
J. F. (Case 4)	Four extremities and trunk	Blurred vision	Day 11	Day 80 Duration: 69 days	Yes	150-190 / 85-100	...	..	...
H. H. (Case 5)	Four extremities and trunk	Diplopia and blurred vision	Day 23	Day 163 Duration: 140 days	Yes	130-160 / 85-95	600	0	206

TABLE 2.—*Ophthalmological Findings in Five Cases in Which Papilledema Developed During Convalescence from Anterior Poliomyelitis*

Patient	Disk Elevation, D.	Cupping	Vessels: Arterioles	Vessels: Veins	Hemorrhages	Visual Acuity
G. H.	4	None	Narrow	.....	Yes	Normal
R. C.	2	None	....	Distended	No	Normal
S. S.	3	None	....	Distended	No	Normal
J. F.	3	None	Normal	.....	No	Normal
H. H.	4	None	Normal		Yes	Normal

muscles were present in each patient as his disease progressed, and each patient still has significant selective muscular wasting and weakness at the time of this report, 9 to 20 months after the onset of acute poliomyelitis.

Table 2 shows the changes in the optic fundi noted in each patient. The findings noted on ophthalmological examination of these patients were indistinguishable from those seen in optic neuritis. However, the presence of normal visual acuity in each patient, as determined by having him read standard fine-print testing cards, and the elevated spinal fluid pressures in each of three patients appeared to indicate that the changes in the optic fundi were the result of increased intracranial pressure and hence represented true papilledema. Since two of the patients had normal arterial blood pressures, it was thought that systemic arterial hypertension was not

responsible for the production of the papilledema. Similarly, obstruction of venous return from the head due to tight respirator collars was not seriously considered, since two of the patients had never been in a respirator and papilledema persisted in two of the others after they no longer needed the respirator.

Repeated neurological examinations revealed only evidence of the original anterior horn cell disease except for the pathological changes in the eyegrounds. Electroencephalograms revealed no specific abnormalities in any of the three patients from whom they were obtained.

Appearing mainly in the convalescent stage of poliomyelitis, papilledema was a benign, self-limited complication, perhaps reflecting generalized postinfectious edema of the central nervous system.

SUMMARY

Papilledema was observed in five severely paralyzed patients in the convalescent stage of acute poliomyelitis. Appearing from 11 to 48 days after the onset of the illness and lasting from 13 to 140 days, it was a benign and self-limited complication.

Each patient complained of double vision, and one had associated headache. The visual acuity and visual fields were normal in each of the five patients, and the spinal fluid pressure was elevated in the three patients in whom it was measured. It is likely that papilledema in these patients represented part of a generalized edema of the central nervous system associated with infection.

BOECK'S SARCOID WITH INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM

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NEW YORK

SINCE Boeck[1] first published his original description of sarcoid, in 1899, approximately 1,500 cases have been recorded in the literature. The disease has been reported from many European countries and in increasing numbers from this country, where a high percentage of patients are Negroes.

In general, the disease is a chronic, low-grade, granulomatous process of unknown cause, with fever, malaise, loss of weight, anorexia, and special symptoms or signs referable to involvement of one or more organs of the body. Common manifestations are lesions of the skin, enlargement of lymph nodes, parotitis, visual loss associated with uveitis (the last two being sometimes referred to as uveoparotid fever), and lesions in the lung, often found on routine chest films without symptoms. Elevation of the blood globulin, x-ray changes in the lungs and phalanges, a negative reaction to the tuberculin test, and a positive reaction to the Kveim test are the commonest laboratory findings. The characteristic microscopic feature of the lesion is the formation of "tubercles" with epithelioid cells, lymphocytes, and occasional giant cells without evidence of caseation. The lesions have been called "noncaseating tuberculosis."

The etiologic agent in this disease is unknown. The tubercle bacillus has been incriminated because of the frequent association with, or termination of the disease in, tuberculosis. However, no convincing proof of the relationship has been reported, and the bacillus cannot be recovered with any consistency from patients with the disease. Thorough postmortem studies of a number of cases have failed to reveal organisms.

Clinically, Boeck's sarcoid is often difficult to distinguish from tuberculosis because of the similarity of symptoms and signs in the two diseases. Relatively good health in the face of extensive lesions, chronicity with a tendency to spontaneous remissions, elevated blood globulin, negative cutaneous reactions to tuberculin, and x-ray changes in the phalanges are the findings important in differential diagnosis. A biopsy of the lesions is often of considerable assistance. Several comprehensive reviews of the disease have appeared in the recent literature.[2]

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1. Boeck, C.: Multiple Benign Sarcoid of Skin, J. Cutan. & Genito-Urin. Dis. **17**:543-550, 1899.

2. (*a*) Freiman, D. G.: Medical Progress: Sarcoidosis, New England J. Med. **239**:664-671, 709-716, 743-749, 1948. (*b*) Longcope, W. T.: Sarcoidosis on Besnier-Boeck-Schaumann Dis-

INVOLVEMENT OF THE NERVOUS SYSTEM

Although the central nervous system is not a common site for lesions of Boeck's sarcoid, at least 51 cases have been reported in the literature. In addition, three cases of manifestations of involvement of the central nervous system have been encountered recently at the Neurological Institute of New York. The occurrence of cerebrospinal-fluid abnormalities in two of these three cases lend additional presumptive evidence as to the nature of the disease.

In Boeck's sarcoid the peripheral nervous system [3] is more commonly involved than is the central nervous system. Signs and symptoms of peripheral-nerve involvement include reflex changes, sensory loss, and cranial nerve palsies. Bell's palsy, unilateral or bilateral, is the commonest of the cranial nerve palsies. Lesions of the optic nerve and of the 8th, 9th, and 10th cranial nerves have also been reported.

In several of the 51 cases with involvement of the central nervous system autopsy has been performed.[4] Lesions have been found in the pituitary gland, hypothalamus, optic nerves, and chiasm [5]; the dura [6]; the tentorium; the retina,[7] and the brain meninges. Several of the patients died suddenly,[2b,f] without previous complaints, and autopsy showed widespread sarcoid lesions in the central nervous system.

The clinical symptoms and signs of involvement of the central nervous system were varied.[8] Headache, visual complaints, confusional states, and various motor and sensory deficits were common. Eight patients experienced one or more generalized seizures at some time during their illness. Hemiplegia, cerebellar signs, reflex changes, the Babinski sign, and sensory deficits were the common findings.

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ease, J. A. M. A. **117**:1321-1327 (Oct. 18) 1941. (*c*) Michelson, H. E.: Sarcoidosis: Review and Appraisal, ibid. **136**:1034-1039 (April 17) 1948. (*d*) Pautrier, L. M.: Sarcoidosis, Brit. J. Tuberc. **42**:1-7, 1948. (*e*) Reisner, D.: Boeck's Sarcoid and Systemic Sarcoidosis (Besnier-Boeck-Schaumann Disease): Study of 35 Cases, Am. Rev. Tuberc. **49**:289-307, 437-462, 1944. (*f*) Ricker, W., and Clark, M.: Sarcoidosis: Clinicopathologic Review of 300 Cases, Including 22 Autopsies, Am. J. Clin. Path. **19**:725-749, 1949. (*g*) Riley, E. A.: Boeck's Sarcoid: Review Based upon Clinical Study of 52 Cases, Am. Rev. Tuberc. **62**:231-285, 1950.

3. (*a*) Levin, P. M.: Neurological Aspects of Uveo-Parotid Fever, J. Nerv. & Ment. Dis. **81**:176-191, 1935. (*b*) Colover, J.: Sarcoidosis with Involvement of the Nervous System, Brain **71**:451-475, 1948.

4. (*a*) Rubin, E. H., and Pinner, M.: Sarcoidosis: One Case Report and Literature Review of Autopsied Cases, Am. Rev. Tuberc. **49**:146-169, 1944. (*b*) Zollinger, and von Meyerburg: Über eigenartige perivaskuläre Granulomatose des Gehirns, Schweiz. med. Wchnschr. **72**:825, 1942. (*c*) Longcope.[2b] (*d*) Erickson, T. C.; Odom, G. L., and Stern, K.: Boeck's Disease (Sarcoid) of Central Nervous System: Report of Case with Complete Clinical and Pathologic Study, Arch. Neurol. & Psychiat. **48**:613-621 (Oct.) 1942.

5. Reis, W., and Rothfeld, J.: Tuberkulide des Sehnerven als Komplikation von Hautsarkoiden vom Typus Darier-Roussy, Arch. Ophth. **126**:357-366, 1931.

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7. (*a*) Naumann.[6] (*b*) Walsh, F. B.: Ocular Importance of Sarcoid: Its Relation to Uveoparotid Fever, Arch. Ophth. **21**:421-438, 1939.

8. (*a*) Colover.[3b] (*b*) Roos, B.: Cerebral Manifestations of Lymphogranulomatosis Benigna (Schaumann) and Uveoparotid Fever (Heerfordt), Acta med. scandinav. **104**:123-130, 1940. (*c*) Waldenström, J.: Some Observations on Uveoparotitis and Allied Conditions with Special Reference to Symptoms from the Nervous System, ibid. **91**:53-68, 1937.

Papilledema occurred in several instances.[9] Visual-field defects have been reported in association with lesions in the neighborhood of the optic chiasm. Everts[10] reported a patient with symptoms of increased intracranial pressure and a homonymous hemianopsia. A large sarcoid tumor of the occipital lobe was observed at operation. Four years later the patient was examined because of sarcoid lesions of the skin, and the spinal fluid was found to be abnormal[11] (Table 3).

Lesions of the Pituitary and Hypothalamus.—Diabetes insipidus was a prominent symptom in 18 of the 51 reported cases with involvement of the central nervous system.[12] In 2 of the 18 cases an adiposogenital syndrome was also exhibited.[13] Three additional patients had only the latter syndrome.[14] All patients of this group had a biopsy diagnosis of sarcoid, and many had lesions outside the nervous system. In six patients on whom autopsy was performed, pituitary and hypothalamic lesions were found. Coleman and Meredith[15] reported a woman with bitemporal hemianopsia and other symptoms characteristic of a pituitary adenoma, together with x-ray changes in the sella turcica. The tumor was removed, and the microscopic picture was consistent with a diagnosis of sarcoid.

Recently a patient with diabetes insipidus was studied at the Presbyterian Hospital. A report of this case follows.

Case 1 (982765).—O. G., a Puerto-Rican jockey aged 19, was admitted to the hospital in March, 1950, because of polyuria and polydipsia, of four-years' duration, and roentgenological evidence of diffuse pulmonary infiltration. At the age of 15 he noted nocturia associated with excessive thirst and frequency of urination during the day. He consumed about 10 glasses of fluid a day and had micturition once a night until six months prior to admission, when his intake increased to 25 glasses a day and his micturition to three to four times a night. X-ray examina-

9. Colover.[3b] Reis and Rothfeld.[5] Roos, B.: Über das Vorkommen der Schaumannschen benignen Lymphogranulomatose (des Boeckschen benignen Miliarlupoids) bei Kindern, Ztschr. Kinderh. **59**:280-302, 1937. Lewis, G. E.: Sarcoidosis: Some Speculations as to the Stages of Infection in General, Brit. M. J. **1**:552-554, 1941.

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11. Everts, W. H.: Personal communication to the author.

12. (*a*) Longcope.[2b] (*b*) Levin.[3a] (*c*) Walsh.[7b] (*d*) Flandin, C.; Parat, M., and Poumeau-Delille, G.: Sarcoïdes noueuses disséminées avec diabète insipide associé, Bull. et mém. Soc. med. hôp. Paris **52**:1423-1426, 1936. (*e*) Jersild, M.: Diabète insipide au cours de sarcoïdes de Boeck, Ann. dermat. et syph. **10**:641-643, 1939. (*f*) Leitner, St. J.: Diabetes insipidus bei der epithelioidzellingen Granulomatose, Schweiz. med. Wchnschr. **75**:511-520, 1945. (*g*) Lesné, E.; Launay, C., and Seé, G.: Diabète insipide au cours d'une maladie de Besnier-Bœck, Bull. et mém. Soc. méd. hôp. Paris **51**:1137-1146, 1935. (*h*) Posner, I.: Sarcoidosis: Case Report, J. Pediat. **20**:486-495, 1942. (*i*) Sands, I. J., and Riley, H. A.: Boeck's Sarcoid with Neurologic Manifestations, Tr. Am. Neurol. A. **68**:57-63, 1942. (*j*) Tillgren, J.: Diabetes Insipidus as Symptom of Schaumann's Disease, Brit. J. Dermat. **47**:223-229, 1935. (*k*) Schaumann, J.: Lymphogranulomatosis Benigna in Light of Prolonged Clinical Observations and Autopsy Findings, ibid. **48**:399-446, 1936.

13. Kraus, E. J.: Sarcoidosis (Besnier-Boeck-Schaumann's Disease) as Cause of Pituitary Syndrome, J. Lab. & Clin. Med. **28**:140-146, 1942. de Morsier, G., and Franceschetti, R.: La neuro-uvéo-parotidite: Maladie de Heerfordt avec syndrome hypothalamique, Rev. neurol. **69**:688-692, 1938.

14. Doub, H. P., and Menagh, F. H.: Bone Lesions in Sarcoid: Roentgen and Clinical Study, Am. J. Roentgenol. **21**:149-155, 1929. Toulant, P., and Morard, G.: A propos d'un cas d'uvéo-parotidite (syndrome d'Heerfordt), Arch. opht. **53**:321-345, 1936. Glass, S. J., and Davis, S.: Granuloma of Pituitary Associated with Panhypopituitarism, J. Clin. Endocrinol. **4**:489-492, 1944.

15. Coleman, C. C., and Meredith, J. M.: Diffuse Tuberculosis of Pituitary Gland Simulating Tumor with Postoperative Recovery, Arch. Neurol. & Psychiat. **44**:1076-1085 (Nov.) 1940.

tion of the chest three months before his admission revealed diffuse pulmonary infiltration, but no organisms could be obtained from the sputum or gastric washings. Two months later, the x-ray appearance had not changed, and the patient was asymptomatic except for mild fatigue and anorexia. Two years before his admission the patient's mother had had the onset of pulmonary tuberculosis, requiring sanatorium care.

On examination the patient did not appear ill. Except for cervical and axillary adenopathy and atrophy of the left testis, there were no significant physical findings. The neurological status was normal.

Laboratory Data.—Blood studies showed 13 gm. of hemoglobin per 100 cc., 4,810,000 red cells, and 9,600 white cells, with a differential count of 58% polymorphonuclear leucocytes, 26% lymphocytes, 11% eosinophils, 3% monocytes, and 2% basophils. The sedimentation rate (Westergren) was 10 mm. in one hour; the Mazzini reaction of the blood was negative. Serum proteins measured 7.7 gm. per 100 cc., with 4.9 gm. of albumin and 2.8 gm. of globulin per 100 cc. Examination of the stools revealed Endamoeba histolytica, Endamoeba nana cysts, hookworm, and Trichuris ova. Cerebrospinal fluid studies showed normal pressure, no cells, a protein content of 31 mg. per 100 cc., and a negative Kolmer reaction. The sputum contained no acid-fast bacilli, fungi, or other organisms. The electroencephalogram, consisting of 16-lead, monopolar and bipolar recordings, showed no focal signs. Irregular, medium-voltage, 3-to-5-cps activity appeared in all leads in response to hyperventilation. Roentgenograms of the chest showed numerous discrete shadows of increased density throughout both lung fields, including the apex and periphery. A skeletal survey of the skull, spine, shoulders, and hands showed no evidence of disease. The reaction to the tuberculin test was negative in 1:1,000 dilution. Skin tests for blastomycosis, histoplasmosis, and coccidioidomycosis gave negative results. A Kveim test gave a negative reaction. Biopsy of a cervical lymph node led to the diagnosis of "chronic lymphadenitis."

Clinical Course.—After treatment for his parasitosis, the eosinophil count returned to normal. The results of two dehydration tests and an infusion of hypertonic saline were felt to be consistent with diabetes insipidus, the specific gravity of the urine never exceeding 1.006. A specific gravity of 1.029 and a marked decrease in polyuria followed injections of vasopressin U. S. P. He was discharged with instructions to continue vasopressin therapy, and, when seen in October, 1950, he was feeling well. A chest film at this time showed that the lesions previously described were unchanged.

Comment.—The x-ray changes in the chest were consistent with either miliary tuberculosis or sarcoidosis. However, the lack of clinical symptoms, the normal sedimentation rate, and the negative reaction to tuberculin, in spite of the non-specific biopsy findings and negative Kveim reaction, made the diagnosis of sarcoidosis the more likely. It is assumed that the diabetes insipidus was caused by a sarcoid lesion of the pituitary gland.

Meningeal Lesions.—Sarcoid lesions have been found in the meninges at autopsy in a number of cases, and several cases have been reported in which the clinical course was that of subacute or chronic meningitis.

Tepper [16] reported the case of a youth aged 17 who, after five days of malaise, anorexia, frontal headache, and misty vision, had onset of fever and bilateral iridocyclitis. One week later, both parotid glands became enlarged; bilateral facial paralysis appeared, and the tendon reflexes were found to be absent. There were pleocytosis, an elevated protein level, and a decreased chloride content of the cerebrospinal fluid. After three weeks the symptoms gradually began to subside, and the spinal fluid returned to normal. He was completely well two months after the onset of symptoms.

Waldenström [8c] reported the case of a woman aged 52 whom he regarded as suffering from "benign miliary tuberculosis." The patient complained of headache

16. Tepper, R.: Uveoparotid Syndrome (Heerfordt's disease), Brit. M. J. **2**:1034, 1947.

and anorexia and was so lethargic that she was at first considered to have encephalitis. She had a tremor of the fingers and hyperalgesia over one-half of the body. One month later there was a bilateral Babinski sign. Biopsy of an enlarged parotid gland gave findings consistent with the diagnosis of sarcoid, and no organisms were found. There were pleocytosis and an elevated globulin content of the cerebrospinal fluid. Guinea pigs inoculated with spinal fluid did not show acid-fast bacilli. For several weeks the patient was acutely psychotic, with confusion and hallucinations. Over the course of the next several months multiple neurological signs developed, but gradually disappeared. Ten months after the onset of symptoms she was completely well and showed no residual neurological signs.

Erickson, Odom, and Stern [4d] reported an autopsy-proved case of meningoencephalitis due to sarcoidosis. The patient had signs of increased intracranial pressure, and the cerebrospinal-fluid-protein content was increased. Exploration of the posterior fossa revealed adhesive arachnoiditis, and at autopsy the lesions in the meninges were found to be sarcoid. No organisms were seen.

Ernsting and Sillevis Smitt [17] reported the case of a patient with an enlarged liver, convulsive seizures, multiple neurological signs, including a Kernig sign, and typical laboratory evidence of sarcoidosis. The spinal fluid showed an increase in cells and protein, and on two occasions the sugar was 40 and 47 mg. per 100 cc. The patient survived two years after the onset of symptoms, but an acute psychosis, status epilepticus, and coma developed terminally. Autopsy was not performed.

Colover [8b] reported the case of a woman with headaches, vomiting, mild fever, and papilledema. A ventriculogram demonstrated internal hydrocephalus. Exploration of the posterior fossa showed thickening of the arachnoid. Biopsy of the arachnoid led to the diagnosis of sarcoid. The spinal-fluid sugar was low (17 to 40 mg. per 100 cc.) on repeated examinations over a period of many months. She recovered without specific therapy, and no organisms were ever found.

Two patients with a low sugar content of the cerebrospinal fluid in association with sarcoid of the central nervous system have been encountered at the Neurological Institute of New York.

CASE 2 (480214).—N. L., a Negro barber aged 48, was first admitted to Presbyterian Hospital in February, 1936, because of epigastric pain, occipital headache, vomiting, loss of weight, and scaly lesions of the skin. The patient had been well until approximately two years prior to admission, when he began to have epigastric pain after meals. The pain became progressively severer, and for the eight months preceding admission he had frequent vomiting and a loss of weight of 45 lb. (20.4 kg.). For about a year he had noted scaly lesions of his forehead, scalp, nose, and ears, and soon after these first appeared he began to have severe frontal and occipital headaches, associated with dizziness and drowsiness. During the six months prior to admission he also experienced severe night sweats and cough, with occasional hemoptysis. One half-sister had died of tuberculosis 16 years previously. He admitted to a moderate intake of alcohol for at least 18 years.

On physical examination, the temperature was 100 F., the pulse rate 95, and the blood pressure 130/95. Scaly lesions of the skin were present over the forehead, scalp, nose, and ears. The liver was enlarged to the level of the umbilicus, but the spleen was not palpable. The pupils were unequal and reacted sluggishly to light. There was partial deafness of the left ear (said to have been present for years after a skull fracture).

Laboratory Data.—Blood studies revealed 85% hemoglobin, 4,500,000 red cells, and 4,200 white cells, with a differential count of 66% polymorphonuclear leucocytes, 28% lymphocytes,

17. Ernsting, W., and Sillevis Smitt, W. G.: Neurologische verschijnselen bij de ziekte van Besnier-Boeck-Schaumann, Geneesk. bl. klin. en lab. prakt. **41**:1-40, 1944.

3% monocytes, 2% eosinophils, and 1% basophils. Urinalysis showed a specific gravity of 1.032, no albumin or glucose, and no sediment. The sedimentation rate (Westergren) was 98 mm. in one hour. The Wassermann reaction of the blood was negative. Serum proteins measured 9.0 gm. per 100 cc., with 3.4 gm. of albumin and 5.6 gm. of globulin per 100 cc. The cholesterol content of the serum was 269 mg. per 100 cc. The serum alkaline phosphatase measured 14.7 Bodansky units. The sulfobromophthalein test showed 15% retention after 30 minutes. The reaction to the Frei test was negative. Repeated examinations of the sputum did not reveal acid-fast bacilli. The roentgenogram of the chest was normal.

Lumbar Puncture (Table 1): The initial puncture was traumatic. There were, however, 6,000 white cells per cubic millimeter, of which 90% were lymphocytes. The globulin was increased, and the Wassermann reaction was negative.

During the two months of hospitalization he had spiking afternoon temperatures, averaging 101 F., but he slowly improved without specific therapy and was discharged, complaining only of mild occipital headache and occasional vomiting. In October, 1936, two skin biopsy specimens were diagnosed as sarcoid, and a tuberculin skin test in a dilution of 1:1,000 gave a negative reaction. A course of radiotherapy improved the cutaneous lesions. All symptoms recurred in February, 1937, but there were no changes in the physical or laboratory findings, and he again improved after one month of hospitalization.

In July, 1938, he returned complaining of his previous symptoms, together with stiffness and soreness of the neck and the sudden onset of vertigo, tinnitus, and loss of hearing in the right

TABLE 1.—*Cerebrospinal Fluid Findings in Case 2 (N. L.) with Sarcoidosis of the Central Nervous System*

Date	Pressure, Mm. H_2O	Cells/Cu. Mm.* P	Cells/Cu. Mm.* L	Protein, Mg./ 100 Cc.	Sugar, Mg./ 100 Cc.	Chlorides, Mg./ 100 Cc.	Other Findings
2/22/36	..	6,000 (?) 10%	90%	Globulin positive	..	...	Wassermann reaction negative
8/19/38	55	..	18	500	32	722	Colloidal gold curve 5544333221
9/20/38	0	..	4	500	..	...	Complete manometric block
11/16/39	85	2	8	350	28	...	Manometric system open
9/24/40	..	..	..	120	..	676	Wassermann reaction negative

* P indicates polymorphonuclear leucocytes; L, lymphocytes.

ear. Headache and intermittent vomiting had persisted since his first admission. Physical examination revealed nothing new except for the appearance of enlarged posterior cervical lymph nodes. On neurological examination the gait was observed to be broad-based, the patient showing a tendency to sway to the left in walking and in the Romberg position. The reflex, motor, and sensory systems were intact. The pupils were irregular, unequal, and almost fixed to light. There was paresis of the left sixth cranial nerve. Nystagmus was present on lateral gaze, and there was partial bilateral deafness. Hepatic function tests again revealed moderately severe damage. Lumbar puncture showed complete manometric block. The fluid contained 18 lymphocytes per cubic millimeter, and 500 mg. of protein, 32 mg. of sugar, and 722 mg. of chlorides, per 100 cc.

A diagnosis of sarcoid lesions of the posterior fossa was made. In view of the lack of definite evidence of increased intracranial pressure, a course of roentgen therapy (6,000 r) was directed to the posterior fossa through six fields. After treatment, the headache disappeared, and the hearing deficit and other symptoms were subjectively improved. He was discharged in October, 1938, with only slight ataxia and a hearing deficit.

During the next year he received two additional courses of roentgen therapy: one for pain and hypesthesia over his back and the other for frontal headache. On both occasions his symptoms were improved after treatment. However, in November, 1939, hoarseness and dysphagia developed, along with a return of dizziness, tinnitus, occipital headache, and weakness of the legs. Neurological findings were essentially the same as on his previous admission except for evidence of thickening and paresis of the left vocal cord. At this time the sulfobromophthalein retention was 50%. Caloric tests revealed a "dead" right labyrinth, whereas previous tests had

shown only impairment. Cerebrospinal-fluid studies showed normal manometric values, 10 cells per cubic millimeter, 350 mg. of protein, and 28 mg. of sugar, per 100 cc. Because of pain in the pelvis, although no changes were seen on x-ray pictures, the patient was given 1,500 r to that region, with dramatic relief of pain.

After discharge he moved to another city, where he was again hospitalized in September, 1940, on account of recurrence of deafness and headache. In addition to the changes found on previous examinations, the tendon reflexes were absent in the lower extremities. The reaction to the tuberculin test was negative in 1:1,000 dilution. The spinal fluid contained 120 mg. of protein and 676 mg. of chlorides per 100 cc.

A remission again occurred, but in October, 1941, he was rehospitalized in a terminal state. At this time there were marked wasting, lethargy, left facial paralysis, and total deafness. A roentgenogram of the chest was normal, and a skin biopsy again led to the diagnosis of Boeck's sarcoid. The course was slowly downhill, but the exact cause of death was not recorded. Permission for autopsy could not be obtained, but the clinical impression was that all the findings in this case could be best explained on the basis of sarcoidosis.

Case 3 (955963).—L. H., a Negro woman aged 25, was admitted to the New York Neurological Institute in May, 1950, because of frequency of urination and staggering gait of 10 weeks' duration. She had been well until about one year prior to admission, when she experienced frontal headaches, followed shortly by pronounced loss of vision, particularly in the left eye. Examination revealed that the loss of vision was due to bilateral iridocyclitis. The results of brucellin, Frei, and tuberculin skin tests were negative. In August, 1949, itchy lesions appeared on the skin of her fingers, the cause of which could not be determined. These improved with radiotherapy. In September, 1949, the reaction to a Kveim test was read as positive. She continued to lose vision in the left eye, and in January, 1950, amenorrhea developed. About 10 weeks before admission she noted unsteadiness of gait, which progressed to inability to walk without support. At approximately the same time she experienced frequency of urination. In the history it was noted that the patient and her husband had contracted syphilis in 1947 but had received adequate therapy with penicillin. Subsequent serologic tests of the blood had been negative for syphilis.

On her entry to the hospital in May, 1950, the general physical examination showed nothing unusual except for a temperature of 101.4 F. and enlargement of a few cervical lymph nodes. Neurological examination revealed ataxia of the gait with incoordination in the movements of the lower extremities as shown in the heel-to-knee test. There was minimal weakness of both lower extremities. The tendon reflexes were barely obtainable. Extensor plantar responses were obtained bilaterally. Sensation was intact except for inconstant slight impairment of position and vibration sense in the lower extremities. The cranial nerves were normal except for residual evidence of apparently inactive iridocyclitis. Vision in the left eye was limited to light perception.

Laboratory Data.—Blood studies showed 13 gm. of hemoglobin per 100 cc., 4,270,000 red cells, and 7,100 white cells, with a differential count of 62% polymorphonuclear leucocytes, 34% lymphocytes, 2% eosinophils, and 1% monocytes and basophils each. The sedimentation rate (Westergren) was 26 and 16 mm. in one hour on two occasions. Urinalysis showed a specific gravity of 1.020, a negative reaction for albumin and glucose, and absence of sediment. The fasting blood sugar was 90 mg. per 100 cc. Serum proteins measured 7.8 gm. per 100 cc., with 4.7 gm. of albumin and 3.1 gm. of globulin per 100 cc. The reaction to the tuberculin test was negative in a dilution of 1:100. Roentgenograms of the chest, skull, and hands were normal. The electroencephalogram was normal. Lumbar puncture revealed an initial pressure of 160 mm. of spinal fluid, with normal dynamics; 51 white cells, 80% of which were lymphocytes; a total protein of 234 mg. per 100 cc.; a negative reaction to the Kolmer test, and a normal colloidal gold curve. On numerous subsequent examinations the sugar content (Table 2) varied from 23 to 29 mg. per 100 cc. and the chloride content was reduced. Cultures of the spinal fluid yielded no organisms, including acid-fast bacilli and fungi. Four guinea pigs inoculated with spinal fluid showed no acid-fast bacilli. Section of a cervical lymph node revealed destruction of its architecture by a granulomatous process. This process consisted of numerous tubercles without caseous centers. Surrounding a central zone of epithelioid and giant cells were a few lymphocytes. In the center of some of the nodules was a homogeneous, pink-staining material, which apparently was fibrin. No fungi or foreign-

body material was found. Since there was no caseation, the pathologist considered that the lesion should be classified as sarcoid unless a definite etiological agent could be established.

Throughout her hospital course she had daily elevations of temperature to 101 F. However, in spite of her abnormal spinal fluid, she appeared relatively well except for her difficulty in gait. A course of 10,000,000 units of penicillin, followed by streptomycin, 2 gm. daily for two weeks, was given, without effect on the elevations of temperature, spinal fluid abnormalities, or neurological signs. Corticotropin, 100 mg. daily for two weeks, had no beneficial effect, and she was discharged as unimproved after six weeks of hospitalization.

In January, 1951, she was admitted to another hospital, where her neurological status was approximately the same as noted above except that there was impairment of pain, touch, and vibratory sensibilities below the level of the second thoracic dermatome. The globulin fraction of the blood ranged from 3.8 to 4.1 gm. per 100 cc., and the reaction to a tuberculin test was negative in a 1:100 dilution. At this time changes suggestive of sarcoidosis appeared in the roentgenograms of her chest and hands. Biopsy of a lymph node again led to the diagnosis of sarcoid. The spinal fluid again showed increased cells and protein, and the sugar content was reduced, being as low as 10 mg. per 100 cc. on one occasion. The blood sugar levels ranged

TABLE 2.—*Cerebrospinal Fluid Findings in Case 3 (L. H.) with Sarcoidosis of the Central Nervous System*

Date	Pressure, Mm. H_2O	Cells/Cu. Mm.* P	Cells/Cu. Mm.* L	Protein, Mg./100 Cc.	Sugar, Mg./100 Cc.	Chlorides, Mg./100 Cc.	Other Findings
5/27/50	180	..	60	237	25	...	Wassermann negative
6/ 5/50	170	13	11	264	29	649	G. P. negative†
6/19/50	...	4	46	231	23	674	.....
6/30/50	...	19	75	264	22	657	G. P. negative
7/ 6/50	...	..	51	243	26	663	G. P. negative
7/11/50	...	..	18	224	26	678	G. P. negative
1/20/51	220	3	5	106	25	632	Wassermann negative G. P. negative
2/ 9/51	240	..	2	133	15	655	G. P. negative
3/ 8/51	208	1	2	134	10	...	.....
3/27/51	150	1	14	145	50	726	.....
4/15/51	200	1	4	100	45	702	.....

* P indicates polymorphonuclear leucocytes; L, lymphocytes.
† G. P. indicates guinea pig inoculations.

from 75 to 100 mg. per 100 cc. A course of 7,025 mg. of cortisone was given, without apparent clinical improvement. She was discharged with essentially unchanged neurological findings.

Comment.—In Cases 2 and 3, although direct examination of the nervous system was not accomplished, the diagnosis of sarcoidosis seemed reasonably well established. The patients harbored their disease from two to seven years, with changes in the cerebrospinal fluid indistinguishable from those of tuberculous meningitis, and yet were relatively well for long periods of time. The course of their illness was inconsistent with that of untreated tuberculous meningitis, making that diagnosis unlikely.

COMMENT

The lesions of Boeck's sarcoid have been found in almost every part of the nervous system and vary from chronic meningeal lesions to actual tumor-like masses. In the 51 cases reported in the literature there was no constant group of signs or symptoms which could lead one to describe a "syndrome" for sarcoidosis of the central nervous system. However, when the disease affects the central nervous system, the pituitary gland seems to be particularly liable to damage, as 35% of the reported patients presented symptoms of diabetes insipidus with or at some time

during the course of their illness. It is therefore important to consider sarcoidosis as a possible cause in cases in which diabetes insipidus is a symptom.

Paralysis of the seventh cranial nerve is rather common in this disease, both in patients with and in patients without evidence of involvement of the central nervous system. It frequently accompanies the parotitis but is not considered to be the result of pressure on the nerve by the swollen gland, because it has occurred in several instances prior to development of the parotitis. Visual complaints are common in patients with sarcoidosis and are usually related to the uveitis, but less often are due to invasion of the retina, optic chiasm, or optic radiations. Ophthalmoscopic examination may reveal lesions in the retina, optic neuritis, or papilledema. The last is usually related to increased intracranial pressure.

Other neurological signs and symptoms are inconstant and depend on the sites of the lesions. In patients whose lesions were primarily meningeal, headache,

TABLE 3.—*Abnormal Cerebrospinal Fluid Findings in Patients with Sarcoidosis of the Central Nervous System*

Author	Cells,* per Cu. Mm.	Protein, Mg./100 Cc.	Sugar, Mg./100 Cc.	Chlorides, Mg./100 Cc.
Coleman and Meredith [15]	3	....	88	692
Colover [3b]	10-162	50-220	17-40	680-720
Erickson, Odom, and Stern [46]	3	372	....	....
Ernsting and Sillevis Smitt [17]	27-52	528-720	40, 47	....
Everts (after 4 yr.) [11]	....	340	105	....
Levin [3a]	1	90	55	....
Naumann [6]	12	Increased	....	632
Pennell				
Case 2	4-6,000 (?)	120-500	32, 28	676, 722
Case 3	0-94	100-264	10-50	632-722
Sands and Riley [121]	....	224	....	....
Tepper [16]	0-68	90-220	54-78	620-700
Thompson †	9-15	38-50	78	....
Wahlenström [8c]	15-53	Increased	....	....

* In all instances 80 to 100% of the cells were lymphocytes. When more than two determinations were done, the range from the highest to the lowest figures is given.

† Thompson, W. C.: Uveoparotitis, Arch. Int. Med. 59:646-659 (April) 1937.

frequently occipital, was a very common symptom, but nuchal rigidity was rare. It was in this group that the spinal fluid was most abnormal.

The cerebrospinal fluid changes were reported in less than half of the 51 cases reviewed in the literature. In cases in which the lesions were apparently limited to the pituitary gland there were no abnormalities of the cerebrospinal fluid. The majority of patients with lesions elsewhere in the central nervous system had an increase in the cells and protein. The cellular response was always predominantly lymphocytic. Colover [3b] reported that the highest cell count was 162 cells per cubic millimeter. The highest value for the protein was reported by Ernsting and Sillevis Smitt [17]—720 mg. per 100 cc. Some of the spinal fluid findings reported in the literature are listed in Table 3.

The sugar content of the cerebrospinal fluid has been determined in nine cases in which there were abnormalities of the cells and protein content. Of these nine cases, there was a significant lowering of the sugar content in four for a period of several months at some time during the illness (Colover [3b]; Ernsting and Sillevis Smitt,[17] Cases 2 and 3). In six patients the chloride content was determined and was found to be lowered in three instances. In Tepper's case [16] the chlorides were

low but the sugar content was normal. In our Case 2 the chlorides were normal when the sugar was low, but in Case 3 both were lowered together.

Both clinical and pathological evidence suggests that the etiologic agent of sarcoidosis is probably an infectious agent. The fact that the sugar content of the spinal fluid has been found to be reduced in four instances of this disease is significant, in that infections are the only known processes affecting the nervous system which lower the spinal fluid sugar content. This finding, therefore, strongly suggests that the agent responsible for sarcoidosis is infectious in nature.

SUMMARY AND CONCLUSIONS

1. Boeck's sarcoid is a low-grade, chronic disease of unknown origin which may involve any part of the nervous system, producing a multiplicity of symptoms. Fifty-one cases of involvement of the central nervous system have been reported in the literature, and three additional cases are included in this presentation.

2. Diabetes insipidus is the commonest symptom of involvement of the central nervous system, and its appearance should suggest the possibility of the disease. Other signs of involvement of the central nervous system include visual loss, convulsive seizures, confusional states, hemiplegia, cerebellar signs, sensory deficits, and papilledema. A low-grade chronic meningeal reaction may also occur and may be accompanied with a significant reduction of the sugar content of the cerebrospinal fluid. This was reported by two previous authors, and two additional cases are included in the present report.

3. The occurrence of low cerebrospinal-fluid sugar is additional evidence that Boeck's sarcoid is caused by an infectious agent.

FORCED CRYING AND LAUGHING

Treatment with Atropine and Atropine-like Agents

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IN THE course of pharmacologic therapy of a patient who exhibited Parkinsonian phenomena associated with forced crying and laughing, it was observed, as a result of medication, that, together with the diminution in tremor amplitude, there was a definite decrease in the frequency and intensity of the paroxysmal episodes of crying and laughing. On the basis of this observation, a series of nine patients showing the phenomenon of forced crying and laughing were given atropine or atropine-like drugs to determine whether these medicaments might be an effective means for the control or modification of this patterned motor discharge.

The nine patients who exhibited episodic uncontrolled laughing and/or crying were systematically studied before and after the administration of scopolamine hydrobromide U. S. P. (orally) or atropine sulfate (subcutaneously) in doses of 1/150 to 1/100 grain (0.4 to 0.6 mg.) three times a day. In certain cases the patients were placed under medication for three or four days and then kept free from medication for 10 to 14 days. With two patients this cycle was accomplished twice, with two other subjects the cycle of medication and no medication was repeated three times. The patients, during the study interval, were kept under almost constant observation. In each instance, control, base-line observations were made prior to the medication. The frequency and intensity of crying and laughing were observed, along with the average intensity of the detonating stimulus for facial-respiratory motor discharges. In general, the day and night corpsmen, at least one other physician, and I constituted the observation team. The statements of members of the family and friends as to the condition of the patient also influenced the final clinical evaluation of the effectiveness of the drug.

All the patients in this group showed gross clinical evidence of irreversible damage to the cortical and subcortical structures of the brain, usually with an arterial hypertension substrate. Three patients died after the cessation of treatment, the interval varying. The one case in which an autopsy was performed is presented in detail. This case was generally representative of the clinical characteristics and pharmacologic response of the entire series of patients.

REPRESENTATIVE CASE HISTORY

The patient, a farmer aged 62, was known to have had arterial hypertension for at least 12 years preceding his final hospitalization. During the five years prior to his admission to the United States Naval Hospital, Bethesda, Md. on Jan. 14, 1947, he had been subject to at least three or four "strokes." Each was associated with loss of consciousness.

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The patient was admitted by stretcher. His blood pressure at that time was recorded as 220/115 mm. Hg. He did not appear to be in acute distress. He was, however, unable to communicate clearly his wishes to the examiner because of repeated episodes of uncontrollable laughter and crying. The crying pattern most frequently dominated the picture. At no time was tearing prominent.

A study of complex communication function was precluded by the limited educational attainments of the patient. He was basically right-handed in all elementary operations. Verbalization was disturbed by incoordinate motor action of the peripheral speech apparatus. The phonic output was marked by actual distortion of polysyllabic words and, above all, by uncontrolled crying and reiteration of an exclamatory "Oh me!" Occasionally there was disturbed ability to activate the lips and tongue on request. At times, also, he had great difficulty in executing any motor action, even as basic as closing the eyelids. Under these conditions there appeared to be comprehension of the intended motor action but inability to execute the act. The intended motor action was carried out with hesitancy and bewilderment, but not in the absent-minded manner usually observed in the ideational dyspraxias. He experienced some difficulty in properly naming common objects of the environment: A pen was sometimes called a knife, but at other times he recognized and named a pencil, a comb, a flashlight, etc. He was able to name many of the test colors that were shown to him. There was moderate ability to reproduce orally simple words that were presented. He was able to read printed simple words, such as "boy," "man," and "table"; but he could not read any combination of printed words. Writing and copying were not accomplished. The patient was able to carry out simple arithmetical calculations, such as "$25 \times 3 = 75$"; he also recognized that five nickels were equivalent to a quarter. No topognostic difficulties were observed; orientation for right and left was intact.

At all times the patient was aware of his surroundings. The examiner felt that there was no disorientation in space-time (static) or in dynamic time. Recent and remote memory function appeared adequate. He was able to name the days of the week and the months of the year. He failed to recognize or to name familiar musical tunes; although he made a good effort, he was not successful in carrying the tune of "America."

Detailed study of the cranial nerves showed weakness of the lower facial muscles (central type) on the left. This weakness was pronounced in dynamic action, both volitional and emotional. Weak pharyngeal reflexes were elicited. On phonation the uvula was elevated in the midline through a moderate amplitude (often he seemed unable to execute the operation of phonation). He repeatedly stated in partial sentences that he could not swallow, "I am choking to death." On occasion when the tongue was protruded, it was grossly in the midline.

When assisted, the patient was able to stand without falling. He walked only a few steps, and with a shuffling gait. The Romberg sign was elicited, but there was no predilection for laterality of fall. Generalized muscular weakness was evident, but the muscle volume was decreased only in the right upper and lower extremities. Despite the general weakness, muscular tone was not grossly altered. Involuntary motor activity was not observed. The patient was unable to touch the tip of his nose with the index finger of either hand. However, he nearly always touched some part of his face in these attempts. Succession movements of the upper limbs were remarkably disturbed, being affected to a greater extent on the left side.

Sensory perception appeared intact to pinprick; all other modalities were subject to inconstant and conflicting replies. The corneal reflex was active bilaterally. Skin reading and stereognostic function tests gave rise to equivocal responses, which could not be evaluated. He repeatedly indicated correctly that he could perceive vibration stimuli.

The jaw jerk was brisk. All tendon reflexes were more active than normal, particularly on the right side. Abdominal reflexes were absent, but the cremasteric responses were present bilaterally and were approximately equal on the two sides. An equivocal Hoffman sign and a definite Babinski sign were obtained on the right. No confirmatory signs were elicited.

At no time was there incontinence of urine or feces. During hospitalization the patient was cooperative in the daytime, but at night he often disturbed the ward by crying and laughing. He repeatedly insisted that he was "choking to death" and repeatedly demanded to be sent home.

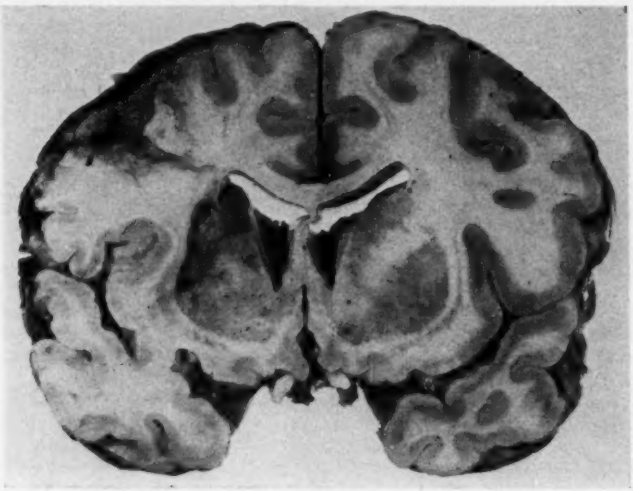
After the oral administration of 1/100 grain (0.6 mg.) of scopolamine hydrobromide three times a day for four days, the patient showed a definite diminution in the frequency and intensity of the uncontrolled facial-respiratory motor discharges. He was again studied in detail on Jan. 23, 1947. He continued to show short, partially stifled episodes of uncontrolled crying, but

there were long intervals during which he was able to converse freely with the examiner. He easily gave a history of his past life; only now and then was the story interrupted by tearless crying. Even the intensity of the discharges seemed much diminished. At this time the dysarthric speech was no longer in evidence, but the dyspraxia of the earlier visit persisted. The basic clinical pattern also remained grossly similar to that observed in the earlier examination. This entire interview was phonographically recorded.

Two days after this study the corpsman on duty noted that the patient was coughing strenuously. He was propped up in bed, but within 15 minutes was observed to be comatose and died shortly thereafter.

At autopsy [1] the trachea was found to be occluded by "two pieces of soft vegetable matter." The distal portions of the upper respiratory apparatus were "markedly edematous." The official cause of death was aspiration of stomach contents, asphyxia, and arteriosclerotic brain disease. He had choked to death!

Examination of the dissected brain showed a well-fixed organ, with no gross hemispheric asymmetry. The convolutions were flattened. A coronal section through the rostral end of the



Coronal section through the rostral end of the corpus striatum, showing old infarct involving the dorsal half of the caudate nucleus, internal capsule, and putamen.

corpus striatum disclosed an old infarct on the right, extending from the ventricle to the external capsule, including the dorsal half of the caudate nucleus, internal capsule, and putamen (Figure). In the same section the right middle frontal gyrus showed a wedge-shaped area of infarction, extending into the corona radiata and the adjacent portion of the inferior frontal gyrus. A section through the optic chiasm showed an irregularly shaped area of softening, approximately 4 mm. in diameter, in the lateral margin of the left thalamus close to, and involving, the internal capsule. Further sections revealed several small cystic infarcts in each thalamus and each corpus striatum. Some of the infarcts were faintly yellow. Section through the splenium of the corpus callosum showed a cortical softening in the right hemisphere at the junction of Areas 19 and 39 of Brodmann. Numerous minute cystic defects were scattered in the basis pontis bilaterally. There was also a small recent hemorrhage on the left. In the lateral portion of the medulla oblongata just medial to the right restiform body was a small grayish area of decreased con-

1. Performed by Dr. John H. Carter, Department of Pathology, United States Naval Medical Center, Bethesda, Md.

sistency. An old infarct was seen in the left dentate nucleus; another was in the right neocerebellum. No focal lesions were observed in the spinal cord. The basilar artery was wide, thick-walled and empty. The larger pial vessels were intensely sclerotic throughout.

Microscopic examination of representative areas demonstrated that the infarcts were not all of the same age.

Summary.—A man aged 62, with a 10-year history of arterial hypertension, had suffered several cerebral vascular accidents in the last five years of life. Laughing and crying dominated the clinical picture. The episodic crying was so intense that it actually impeded the verbalization function. Moderate amnestic aphasia was recognized. A central type of facial weakness was noted on the left. He repeatedly stated that he could not swallow. There was decreased muscle volume on the right, but generalized muscular wasting with asthenia was pronounced. No gross changes in sensory perception were elicited. The tendon reflexes were more active on the right than on the left; a Babinski sign was elicited on the right. Oral administration of scopolamine hydrobromide gave rise to a definite diminution in the frequency and intensity of the episodes of uncontrolled laughing and crying. Autopsy showed that the immediate cause of death was asphyxia due to aspiration of stomach contents. The brain showed multiple infarctions, the largest and most prominent lesions being in the right cerebral hemisphere. Numerous minute cystic defects were scattered bilaterally in the basis pontis.

RESULTS OF STUDY

All the patients in this series showed a minimal to pronounced decrease in the frequency and intensity of forced crying and laughing during the administration of atropine and atropine-like drugs. Usually the beneficial effects were evident within 24 hours. They were ordinarily coincident with the signs of dryness of the mouth and throat and subsequent thirst. During the treatment period it was necessary to keep up morale, as all the patients preferred the crying and laughing episodes to the discomfort of the effect of the medication. Because of this fact, one patient was placed on a regimen of trasentine® (adiphenine; diphenylacetyl-diethylaminoethanol hydrochloride), 50 mg. three times a day. His daughter, his brother, and three of the observers believed that there was a definite decrease in the number of laughing and crying spells during medication. But one member of the observing group believed that there was no change. This patient had three cycles of medication, one with atropine sulfate and two with the adiphenine. It was of interest that the major mode of triggering a clinical response was to ask him to smile. He would generate a weak smile, which would proceed to a grin, and then there would be a chuckle, followed by forced crying. By use of this maneuver, the author "quantitatively" estimated the effectiveness of the drug.

In use of the atropine-like drugs in patients with heart disease it is necessary to keep close watch of the cardiac function. These patients readily have decompensation. Any considerable increase in dependent edema or any definite increase in pulse rate requires an immediate reduction in dosage of the medicament. Through careful observation, none of the patients in this series had a serious toxic effect from the administered drug.

After the cessation of medication, the patients ordinarily showed a lag of two or three days before the crying and laughing became as prominent as it had been

during the premedication studies. In one patient crying was certainly much decreased for several weeks after the course of therapy.

Of course, in a moderately large series of patients it is clear that there are many persons with phasic variations in the frequency and intensity of forced crying and laughing. In the series of cases presented it was noted that when the patients became accustomed to the surroundings, and when their needs were reasonably well supplied, there was often a decreased tendency toward uncontrolled weeping. This was particularly pronounced when an attendant or another patient took an unusual interest in the patient. Because of these environmental factors, it was found necessary to maintain basal conditions rigidly in order to evaluate properly the effectiveness of the medication on the phenomenon under study.

It must be emphasized that in only one patient was there unanimous agreement by the observers that the employed medication repeatedly and remarkably altered the laughing and crying episodes.

COMMENT

The striking phenomenon of uncontrolled laughing and crying has been the subject of beautiful contributions from masters of neurology,[2] but no unified theoretical basis for the clinical action has been established. Davison and Kelman,[3] as well as Oppenheim and Siemerling,[2d] have clearly shown that lesions in many regions of the brain, namely, cortical, corticodiencephalic, diencephalic, and mesencephalometencephalic, are capable of giving rise to clinical episodic, uncontrollable laughing and/or crying. On this basis, the localization of "a center" for forced crying and laughing seems fruitless. It thus appears that certain aspects of the organizational details of brain function must be reevaluated in order to arrive at a first-order approximation to the understanding of the complex activity involved in the process of forced crying and laughing.

It appears that, depending on the organization of the individual brain, a pathologic lesion in a direct action system or in an association area may act as the disrupter of the normally established pattern of reception, or pattern of action, and thereby generate an inappropriate clinical response (for the observers) to a given constellation of ordinarily nonemotionally charged stimuli. From this point of view, one must consider, as did Goldstein,[4] the basic integration pattern of the patient. In this regard, several patients of the present series were said by the family to have always been "soft-hearted, but of course . . . never like this before."

Despite the general amelioration of the phenomenon of forced crying and laughing by the administration of atropine and the atropine-like drugs, the mode of action is not easily determined. From the work of Brenner and Merritt,[5] it

2. (*a*) Mills, C. K.: The Cerebral Mechanism of Emotional Expression, Tr. Coll. Physicians, Philadelphia **34**:147, 1912. (*b*) Brissaud, E.: Rire et pleurer spasmodiques, Rev. neurol. **8**:824, 1900. (*c*) Wilson, S. A. K.: Pathological Laughing and Crying, in Modern Problems in Neurology, New York, William Wood & Company, 1929, p. 260. (*d*) Oppenheim, H., and Siemerling, E.: Mittheilungen über Pseudobulbärparalyse und acute Bulbärparalyse, Klin. Wchnschr. **23**:791, 1886.

3. Davison, C., and Kelman, H.: Pathologic Laughing and Crying, Arch. Neurol. & Psychiat. **42**:595 (Oct.) 1939.

4. Goldstein, K., in discussion on Wechsler, I. S.: Excision of Speech Area Without Resultant Aphasia, Arch. Neurol. & Psychiat. **35**:432 (Aug.) 1937.

5. Brenner, C., and Merritt, H. H.: Effect of Certain Choline Derivatives on Electrical Activity of the Cortex, Arch. Neurol. & Psychiat. **48**:382 (Sept.) 1942.

seems that certain aspects of the electrical activity of the cortical neurones are best explained by invoking the direct action of acetylcholine on the nerve cells. In keeping with this work, Pope and associates [6] have shown that in the region of epileptogenous lesions of the brain there is an increase in the amount of cholinesterase. If it is assumed that the increased cholinesterase is produced to counterbalance a local increase in acetylcholine around the "epileptogenic" lesions, then a priori it appears equally likely that acetylcholine might be increased around any lesion in the brain. The experiments of Essig, Himwich, and their co-workers [7] furnish some evidence on the central interaction of atropine and acetylcholine. They have shown that after the administration (via the carotid artery) of the anticholinesterase drug diisopropyl fluorophosphate, which gives rise to centrally initiated circling movements in laboratory animals, the arterial injection of atropine is able to counteract this circling behavior. Therefore in our experiments, despite the clinically nonepileptogenic nature of the lesions, there is a good probability that atropine exerts centrally a specific antagonistic action on locally accumulated excess acetylcholine. Feldberg [8] invited the temptation to hypothesize just such an atropine-acetylcholine antagonism in discussing the "sedative" action of atropine on the rigidity and tremor of Parkinsonism.

CONCLUSION

Atropine and atropine-like drugs appear to decrease the intensity and frequency of spasmodic laughing and crying, which are the result of irreversible pathologic lesions of the brain.

6. Pope, A.; Morris, A. A.; Jasper, H. H.; Elliot, K. A. C., and Penfield, W.: Histochemical and Action Potential Studies on Epileptogenic Areas of Cerebral Cortex in Man and the Monkey, A. Res. Nerv. & Ment. Dis., Proc. **26**:218, 1947.

7. Essig, C.; Hampson, J. L.; McCauley, A., and Himwich, H. E.: Experimental Analysis of Biochemically Induced Circling Behavior, J. Neurophysiol. **13**:269, 1950.

8. Feldberg, W.: Present Views on the Mode of Action of Acetylcholine in the Central Nervous System, Physiol. Rev. **25**:596, 1945.

PAPILLEDEMA IN THE GUILLAIN-BARRÉ SYNDROME

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PAPILLEDEMA is an infrequently reported finding in the Guillain-Barré syndrome. A recently studied case is reported here, together with a review of the available literature and a discussion of the mechanism of the production of papilledema in the Guillain-Barré syndrome.

Since the original description, in 1916, by Guillain, Barré, and Strohl [1] of "a syndrome of radiculoneuritis with increased spinal fluid protein without cellular response," a rather characteristic clinical picture has come to be known and recognized by the clinician as the Guillain-Barré syndrome. The originally emphasized albuminocytologic dissociation continues to be the most important single diagnostic feature. The protein is always elevated and may exceed 1,000 mg. per 100 cc. Nonspecific alterations in the colloidal gold curve are usually obtained. The composite clinical picture [2] usually includes an antecedent history of infection of the upper respiratory tract. Within a matter of days or weeks the typical syndrome begins with leg and back pain, followed by weakness of the distal extremities. The weakness spreads, and often the proximal musculature becomes most involved. Superficial reflexes are generally normal, but tendon reflexes are decreased or absent. Sensory disturbances are usually very mild or absent. Facial diplegia is common.

Many variations from the more classic description have been noted. Some authors have seen fit to classify the clinical variations, as has De Jong,[3] whose groups include acute cases of short duration with good prognosis, chronic cases, and fatal cases. Baker [4] proposed grouping according to the maximum intensity of the pathologic process and listed abortive and mononeuritic, polyneuritic, myelitic, bulbar, and cerebral forms. The literature is confused by numerous general terms

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1. Guillain, G.; Barré, J.-A., and Strohl, A.: Sur un syndrome de radiculo-névrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire, Bull. et mém. Soc. méd. hôp. Paris **40**:1462 (Oct. 13) 1916.

2. Alpers, B. J.: Clinical Neurology, Philadelphia, F. A. Davis Company, 1946, pp. 157-159. Grinker, R., and Bucy, P.: Neurology, Ed. 4, Springfield, Ill., Charles C Thomas, Publisher, 1949, pp. 674-676. De Jong, R. N.: The Neurologic Examination, New York, Paul B. Hoeber, Inc., 1950, p. 1026.

3. De Jong, R. N.: The Guillain-Barré Syndrome: Polyradiculoneuritis with Albuminocytologic Dissociation, Arch. Neurol. & Psychiat. **44**:1044-1068 (Nov.) 1940.

4. Baker, A. B.: Guillain-Barré's Disease (Encephalo-Myelo-Radiculitis): A Review of 33 Cases, Journal-Lancet **63**:384-398 (Dec.) 1943.

for the syndrome and its variants, including acute infective polyneuritis, myeloradiculitis, neuronitis, polyneuritis with facial diplegia, and radiculoneuritis. The heterogeneity of etiologic and clinical groups has been stressed by De Jong [3] in a historical review preceding his case reports.

Papilledema, though reported in a number of cases, has rarely been emphasized in the clinical picture of the Guillain-Barré syndrome. The only discussions in the standard texts are those of Ford [5] and Walsh.[6] These investigators, in a joint paper,[7] reported on its occurrence in 1946, presenting two cases of the Guillain-Barré syndrome associated with papilledema. Their first patient, a woman aged 26, showed 3 D. of papilledema and complained of headache and blurred vision, though visual acuity and visual fields were normal. The cerebrospinal fluid pressure was 600 mm. of water, and the protein level was 420 mg. per 100 cc. A subtemporal decompression following ventriculographic study relieved the patient's complaints and disk abnormalities. Their second patient, a youth aged 16, had a cerebrospinal fluid pressure of 400 mm. of water and a protein level of 200 mg. per 100 cc. when papilledema of 2 to 3 D. was observed. Headache and vomiting were relieved, but no statement was made as to the course of the papilledema. There was no other evidence of increased intracranial pressure, and no surgical procedure was employed, as the onset of the papilledema was apparently not sudden and no associated hemorrhages or abnormalities of the retinal vessels were noted, such as had been present in their first case.

Prior to this report, Gilpin, Moersch, and Kernohan [8] had described papilledema of 2 to 3 D. in a case of the Guillain-Barré syndrome in a young man. The cerebrospinal fluid pressure was 330 mm. of water, and the protein level was 400 mg. per 100 cc. Note was made of two other cases of the syndrome associated with papilledema, but details of these cases were not reported.

A number of other investigators have reported optic nerve abnormalities in the Guillain-Barré syndrome. Mirus [9] described the case of a man aged 38 with papilledema of 3 D. The cerebrospinal fluid pressure in this case was not mentioned, but the protein was increased. Bassoe [10] reported the case of a girl aged 3 years with the Guillain-Barré or a related syndrome whose cerebrospinal fluid protein was 2,080 mg. per 100 cc. Papilledema developed in this case, and lumbar puncture disclosed evidence of block. The cerebrospinal fluid pressure was 150 mm. of water. The presence of a manometric block casts doubt on the reported diagnosis. De Jong [3] mentioned hyperemia of the optic disks in one case and definite papilledema

5. Ford, F.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1945, p. 650.

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7. Ford, F. R., and Walsh, F. B.: Guillain-Barré Syndrome (Acute Infective Polyneuritis) with Increased Intracranial Pressure and Papilledema: Report of 2 Cases, Bull. Johns Hopkins Hosp. **73**:391-395 (Nov.) 1943.

8. Gilpin, S. F.; Moersch, F. P., and Kernohan, J. W.: Polyneuritis: A Clinical and Pathologic Study of a Special Group of Cases Frequently Referred to as Instances of Neuronitis, Arch. Neurol. & Psychiat. **35**:937-963 (May) 1936.

9. Mirus, E.: Beitrag zur Frage der Stellung des Guillain-Barréschen Syndroms im Rahmen der Polyneuritis, Deutsche Ztschr. Nervenh. **150**:39-69, 1939.

10. Bassoe, P.: Guillain-Barré Syndrome and Related Conditions (Meningoradiculomyelitis and Meningomyeloencephalitis), Arch. Path. **26**:289-296 (July) 1938.

in another, with normal cerebrospinal fluid pressure and 268 mg. of protein per 100 cc. Both cases were classified as acute, with short duration and good prognosis. Pullen and Sodeman [11] described transitory papilledema occurring in a man aged 31, associated with decreased vision. The cerebrospinal fluid pressure was 130 mm. of water, and the protein was over 1,000 mg. per 100 cc. Sanz and Pérez [12] reported the case of a young man in whom slight papilledema developed. The cerebrospinal fluid pressure was not given; the protein was as high as 286 mg. per 100 cc. Chisud and Marquardt,[13] under the title of "Acute Infectious Polyneuritis," reported the case of a man aged 37 with papilledema whose cerebrospinal fluid was under a pressure of 350 mm. of water and had a protein content of 815 mg. per 100 cc. For four months prior to the development of the disk abnormality, the cerebrospinal fluid pressure had been over 200 mm. of water. Lassen and Fog [14] postulated that the occurrence of papilledema in their case of a disturbance diagnosed as polyradiculitis was due to arachnoiditis in the posterior fossa with transitory occlusion of the basal foramina. The cerebrospinal fluid findings were not mentioned. Brock and Davison [15] reported the pathologic findings in a case of fatal "cryptogenic neuropathy." The cerebrospinal fluid pressure was normal in their patient, and the protein was never in excess of 250 mg. per 100 cc. Blurring of the upper disk margins was followed by hemorrhages above the papillae and engorgement of the retinal vessels. Apparently, there was no progression of the fundus abnormalities, despite the fatal course. Perivascular demyelination with slight swelling of the myelin sheaths, occasional perivascular lymphocytic infiltration, and slight perivascular gliosis and astrocytic proliferation were observed in the optic nerve and optic tract. The clinical findings were correlated with this anatomical involvement, which was most intense in the peripheral nerves, followed by that of the roots, cord, diencephalon, and cortex.

Weinberg,[16] Louria and Mandelbaum,[17] Hand and Rudoy,[18] and Shaskan [19] all commented on the occurrence of hazy or blurred disk margins in the Guillain-Barré syndrome. Van Gehuchten [20] reported a case of polyradiculoneuritis with albumino-

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14. Lassen, H. C. A., and Fog, M.: Acute Polyradiculitis, Acta med. scandinav. **115**:117-138, 1943.

15. Brock, S., and Davison, C.: Fatal Cryptogenic Neuropathy, Arch. Neurol. & Psychiat. **58**:559-569 (Nov.) 1947.

16. Weinberg, H. H.: Neuronitis (Encephalo-Myelo-Radiculo-Neuritis), Confinia neurol. **8**:265-274, 1947-1948.

17. Louria, A. L., and Mandelbaum, H.: Acute Infective Polyneuritis Following Pneumonia, J. A. M. A. **115**:1188-1190 (Oct. 5) 1940.

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cytologic dissociation and mild papilledema, but atypical features of this case, as noted by Guillain [21] in a discussion on this report, make questionable its inclusion in the group under discussion in the present paper. Baker [4] described papilledema occurring in the "cerebral form" of the Guillain-Barré syndrome. In his case the cerebrospinal fluid contained 22 cells per cubic millimeter and 58 mg. of total protein per 100 cc. It is questionable whether this case should be considered with other cases of the syndrome showing true albuminocytologic dissociation.

We have had the opportunity of studying a patient with the characteristic findings of the Guillain-Barré syndrome and pronounced papilledema.

REPORT OF A CASE

History.—A. H., a white man aged 38, a bus driver, was admitted to the neurology service of the University Hospital on Aug. 15, 1950. One week prior to admission, the patient awoke with numbness of the soles of both feet. The numbness rose to the level of the umbilicus bilaterally. He also complained of numbness in both hands and forearms and in his face and tongue. As the numbness progressed, he lost bladder sensation. Several days before admission he noticed unsteadiness of gait and complained that he did not know where his feet were going. For a 24-hour period his right eyelid drooped, but this condition cleared and did not recur. Other complaints included constipation, insomnia, anorexia, and a dull headache, centering mainly in the left occipital region, which, though varying in severity, was constantly present for about five days before his admission.

Prior to this illness the patient had always been in good health. There was no family history of nervous or mental disease.

Examination.—On admission, the patient's blood pressure was 128/70, the pulse rate 80, the respiration rate 20, and the temperature 97 F. The general physical examination revealed no abnormalities.

Examination of the cranial nerves revealed coarse nystagmus on lateral gaze to either side. Visual acuity was grossly normal. The optic disks were normal, and the retinal vessels were not engorged. There was evidence of incomplete bilateral facial paralysis of peripheral type. Taste sensation was absent over the anterior surface of the tongue bilaterally. Otherwise the cranial-nerve examination revealed a normal condition, including sensation on the face, where subjectively the patient complained of numbness. Light touch sensibility was normal over the entire body, but pain and temperature sensations were reduced in both feet. Elsewhere there was no change in pain and temperature sensibility, despite the patient's complaint. Vibration sense was slightly reduced in the right ankle. Position and motion sensations were normal. The patient's gait was ataxic. The Romberg sign was positive, the patient falling to the right. Muscle bulk was normal. There were no fasciculations or abnormal involuntary movements. Muscle strength was reduced in the right upper extremity only. Fine and successive movements were impaired in the right hand. The findings in finger-to-nose and heel-to-knee tests were normal. The superficial abdominal and cremasteric reflexes were absent, and the tendon reflexes were uniformly reduced. No abnormal reflexes were elicited.

Laboratory Studies.—Examination of the peripheral blood disclosed 4,000,000 red blood cells, 11.9 gm. of hemoglobin per 100 cc., 7,700 white blood cells, and a normal differential cell count. The urine was normal except for the presence of 15 to 20 white blood cells per high-power field. The sedimentation rate was 12 mm. in one hour, and the hematocrit reading was normal. The reaction to the Kahn test of the blood serum was negative, as was the Watson test for proporphyrins. Other laboratory studies, including determinations of liver function, serum protein, carbon-dioxide-combining power, and serum chlorides, sodium, and potassium, gave normal values. An electrocardiogram revealed only occasional ventricular extrasystoles. Lumbar puncture on admission disclosed clear fluid, under 150 mm. of cerebrospinal fluid pressure, with

21. Guillain, G.: Synthèse générale de la discussion sur les polyradiculo-névrites, J. belge neurol. et psychiat. **38**:325 (April) 1938.

normal dynamic equilibrium. Six lymphocytes were present per cubic millimeter. Chemical studies of the fluid disclosed a normal sugar content, a negative Kahn reaction, a total protein content of 540 mg. per 100 cc., a colloidal gold curve of 0001211000, a mastic curve of 455531, and excessive globulin.

Roentgenograms of the skull and chest showed a normal status. Ophthalmologic consultation disclosed vision to be 6/6 in the right eye and 6/15 in the left eye. Ocular tension was normal, as were the pupillary reactions and extraocular movements. The lens and central media were clear in both eyes. The disks were normal in size, shape, and color. The margins were clear. Venous pulsations were present. Physiologic depression and lamina cribrosa were observed. The macula and peripheral portion of the retina were normal in each eye. The central and peripheral visual fields were normal. The blind spots measured 14.5 by 17 mm. in the right eye and 14 by 17 mm. in the left eye. An audiogram and caloric studies showed a normal condition except for mild perceptive hearing loss bilaterally. An electroencephalogram performed during the fourth month of hospitalization disclosed a mildly abnormal and slightly stereotyped record in regard to amplitude and frequency, consistent with a mild diffuse degenerative condition. In particular, there was nothing in the electroencephalogram to suggest neoplasm.

Course.—Shortly after admission the patient began to complain of generalized aching and weakness of his legs. Within a week after admission, a second examination revealed progression of the weakness of the right arm and marked paresis of both lower extremities. Reduction in sensation to pinprick was noted to the umbilicus and over the face and both forearms. During the second week, the patient was started on treatment with cortisone. The weakness in his legs was then severe. He was unable to stand and continued to complain of severe muscular aching. After five days cortisone therapy was discontinued, as the weakness continued to progress. A lumbar puncture done in the third week of hospitalization showed clear fluid, under a pressure of 195 mm. of cerebrospinal fluid and with a total protein of 624 mg. per 100 cc. Three lymphocytes were present per cubic millimeter. Other studies revealed no change.

During the fourth hospital week the patient had to be placed on a regimen of continuous catheterization, as he had lost all ability to urinate spontaneously. Daily enemas were necessary. His appetite was so poor that supplemental gavage feedings were necessary. Paresis of the right oculomotor nerve developed and cleared after a few days.

After one month the patient's condition stabilized somewhat, and daily physical therapy was started. Lumbar puncture at this time disclosed a pressure of 220 mm. of cerebrospinal fluid and 330 mg. of total protein per 100 cc. Examination showed no abnormality of extraocular movements. There was residual facial diplegia. A slight improvement in strength in the upper extremities was observed, but all movements in the lower extremities remained very paretic. Muscular tenderness was too severe to permit adequate examination. Generalized atrophy was beginning to appear, being severest in the small hand muscles. Tendon reflexes were either absent or very hypoactive.

During the sixth week, a routine examination disclosed bilateral papilledema, although the patient noted no visual disturbances or retrobulbar pain. The right optic disk was elevated about 3 D., and many flame-shaped hemorrhages were seen around and on the disk. There was no physiologic depression or lamina cribrosa. The rest of the retina was normal except for mild macular edema. There was only slight elevation of the left optic disk, but venous pulsations were absent, and two flame-shaped hemorrhages were noted at the disk margins. Vision was 6/6 in the right eye and 6/15 in the left eye, this representing no change since his admission. The visual fields showed enlargement of both blind spots, measuring 23 by 29 mm. in the right eye and 18 by 25 mm. in the left eye. Lumbar puncture at this time disclosed a pressure of 250 mm. of cerebrospinal fluid without any evidence of subarachnoid block. The protein content was 490 mg. per 100 cc.

The papilledema remained pronounced for about two months, but throughout this time there was no subjective or objective visual impairment. Another lumbar puncture, performed in the eighth week of hospitalization, during the height of the papilledema, disclosed a pressure of 150 mm. of cerebrospinal fluid, again without evidence of block.

After about two months the papilledema slowly began to recede, and examination in the sixth month of hospitalization showed only blurring of the disk margins with slight distention of the

veins in both eyes. No spontaneous venous pulsations were present. Acuity was 6/6 in the right eye and 6/15 in the left eye. The visual fields were normal, and the blind spots then measured 15 by 22 mm. in the right eye and 15 by 14.5 mm. in the left eye.

During the last four months, and during the period in which the papilledema appeared and disappeared, the patient's general neurologic status was nearly stationary. Daily physical therapy was given, but at the time of discharge, after six months of hospitalization, both lower extremities were very weak. He was unable to stand even with assistance. Atrophy and hyporeflexia were prominent in both upper and lower extremities, though his strength was considerably better in the arms than in the legs. Deep pain sensation remained increased. The facial diplegia had cleared. Lumbar puncture at the time of discharge yielded clear fluid under a pressure of 100 mm. of cerebrospinal fluid, and containing only 1 cell per cubic millimeter. The total protein was 370 mg. per 100 cc.

The patient was reexamined 11 months after admission to the hospital. He complained of persistent occipital headaches, but, aside from this and generalized weakness, he had no complaints. In particular, he had no difficulty with the bowel or bladder. He was able to shave and dress himself and could stand unsupported for a few minutes at a time. He could walk with crutches.

Examination of the cranial nerves showed no abnormality. The facial diplegia had completely cleared, and taste sensibility was normal. There was slight blurring of the nasal margin of both disks, but there was no elevation and the veins were not distended. No hemorrhages or exudates were seen. Muscular weakness was still evident in all extremities. There was atrophy of the small muscles of the hands and feet, that of the proximal muscles of the extremities being of less degree. Tendon reflexes were absent. Sensation was normal in the upper extremities, but all modalities were decreased in both feet.

Lumbar puncture disclosed fluid under a pressure of 150 mm. of cerebrospinal fluid with normal dynamic equilibrium. Three lymphocytes were present per cubic millimeter. Studies disclosed a total protein of 230 mg. per 100 cc., a colloidal gold curve of 0012332100, a mastic curve of 234221, and a reaction of 4+ for globulin.

COMMENT

The case presented has many of the characteristic features which have come to be considered diagnostic of the Guillain-Barré syndrome. Its interest lies in the presence of marked papilledema. Papilledema, as a review of the available literature shows, has been documented in only nine previous cases. Judging from the poverty of the literature and our own experience, choked disk may be considered either an infrequent finding in the Guillain-Barré syndrome or a frequently overlooked complication.

In the case presented, the papilledema developed in the middle of a protracted course. Unlike most of the previously reported cases, cerebrospinal fluid pressures and protein values in this case can be correlated with careful ophthalmologic studies of visual fields and visual acuity. Few cases in the literature are reported extensively, and these reports do not readily lend themselves to any attempt at analysis of the factors usually considered responsible for the production of papilledema.

It is not the purpose of this paper to review the controversial problem of the mechanism of the production of papilledema. It is, however, pertinent to the present problem to note several of the more generally accepted factors which appear to be involved. Duke-Elder [22] outlined four principal theories: (1) blockage of the normal centripetal flow of tissue fluid from the eye to the brain; (2) venous engorgement, due to pressure on the central retinal vein; (3) forced entrance of

22. Duke-Elder, S.: Text-Book of Ophthalmology, Vol. 3, St. Louis, C. V. Mosby Company, 1941, pp. 2955-2956.

cerebrospinal fluid under pressure into the optic nerve; (4) edema of the optic nerve as part of a general cerebral edema. May [23] stated: "At present it [papilledema] is generally believed to be due to increased intracranial pressure forcing cerebrospinal fluid into the intervaginal space of the optic nerve, causing stasis in the region of the lamina cribrosa and compression of the vessels, resulting in venous engorgement." This statement of the situation follows the early suggestion of Schmidt [24] and the pathologic analysis made by Paton and Holmes.[25] It is also in line with the findings of Lauber [26] and Sobánski,[27] who reported that the ratio of diastolic venous pressure in the retina to diastolic arterial pressure is increased in papilledema. However, Wolff and Davis [28] were unable to produce papilledema by the injection of fluid into the subarachnoid space at pressures compatible with life, as had previously been reported by Cushing and Bordley.[29]

It would appear that the general statement made by May is compatible with most observations, with the possible exception of those made by Wolff and Davis.[28] In addition, May's generalization appears to incorporate three of the four theories noted by Duke-Elder. According to Rea,[30] it was Parinaud who first suggested the fourth hypothesis, namely, that edema of the optic disk is simply a part of generalized edema of the central nervous system.

For the present purpose, it appears safe to state that papilledema is either part of a generalized cerebral edema or the result of venous and lymphatic stasis in the optic disk and anterior layers of the lamina cribrosa. The exact mechanism of the production of this stasis remains in question.

In the cases under discussion it would appear that any or all of the factors noted by Duke-Elder might be responsible for the development of the papilledema. With the exception of four reported cases, the spinal fluid pressure was appreciably elevated. Thus, the possibility of forced entrance of cerebrospinal fluid under pressure into the optic nerve must be considered. In addition, it is necessary to entertain the thesis that the increased spinal fluid pressure leads to compression of the central retinal vein and thus results in venous engorgement. The rather marked hemorrhagic tendency in our own case lends some support to the idea that this factor was present.

The characteristic abnormality of spinal fluid protein in the Guillain-Barré syndrome must be considered in any discussion of the papilledema in that syndrome. Grossly elevated protein values are reported in all cases. It is at least possible that

23. May, C. H.: Manual of the Diseases of the Eye for Students and General Practitioners, Ed. 17, Baltimore, William Wood & Company, 1941, p. 324.

24. Schmidt, H.: Zur Entstehung der Stauungspapille (Neuritis optica intraocularis) bei Hirnleiden, von Graefes Arch. Ophth. **15**:193-197, 1869.

25. Paton, L., and Holmes, G.: The Pathology of Papilloedema: A Histological Study of Sixty Eyes, Brain **33**:389-432, 1910-1911; The Pathology of Papillœdema, Ophth. Soc. U. Kingdom **31**:117-131, 1911.

26. Lauber, H.: Die Entstehung der Stauungspapille, Wien. klin. Wchnschr. **47**:1537-1541 (Dec.) 1934.

27. Sobánski, J.: Der Wert dynamometrischer Untersuchung für die Erklärung der Entstehung der Stauungspapille, von Graefes Arch. Ophth. **137**:84-92 (April) 1937.

28. Wolff, E., and Davis, F.: A Contribution to the Pathology of Papillœdema, Tr. Ophth. Soc. U. Kingdom **51**:170-187, 1931.

29. Cushing, H., and Bordley, J.: Observations on Experimentally Induced Choked Disc, Bull. Johns Hopkins Hosp. **20**:95-101 (April) 1909.

30. Rea, R. L.: Neuro-Ophthalmology, Ed. 2, St. Louis, C. V. Mosby Company, 1941, p. 90.

the increased protein interferes with the assumed normal centripetal flow of tissue fluid from the eye to the brain and thus promotes stasis and edema of the optic disk and anterior lamina cribrosa. Furthermore, the increase in spinal fluid protein must be considered in any statement concerning cerebrospinal fluid pressure. It is generally held that the pressure reading obtained by lumbar manometry is a direct recording of the intracranial cerebrospinal fluid pressure plus the weight of the column of fluid above the intrathecal needle. Marked increases in spinal fluid protein will result in a definite increase in the weight of the column, and it might be argued that the elevated spinal fluid pressures recorded are not true indexes of the intracranial pressure. In the cases reported, however, there is no valid correlation between the recorded spinal fluid protein and the recorded lumbar pressure of the spinal fluid. No record of intraventricular or cisternal pressure is available, nor are data available with which to evaluate the Ayala indexes, and thus to speculate regarding the factor of increased volume of cerebrospinal fluid.

While the pathology of the Guillain-Barré syndrome is not entirely clear, Lichtenstein [31] and others have stressed the presence of edema in the peripheral nerves and spinal roots. In addition, some edema of the central nervous system has been noted. These facts make it necessary to consider whether or not the observed papilledema can be explained simply as a part of the generalized edema of the peripheral and central nervous systems. This explanation would cover those cases reported with normal spinal fluid pressures.

Despite the fact that the neuropathology of the Guillain-Barré syndrome is marked by the absence of inflammatory changes, it is necessary to consider the possibility of optic neuritis. We believe that the absence of visual complaints and the relatively mild changes in visual acuity and visual fields in our own case rule out the consideration of anything but a true papilledema.

We believe that it is impossible, on the basis of the present case, or of the small number of cases in the literature, to come to a satisfactory conclusion regarding the mechanism of the development of papilledema in the Guillain-Barré syndrome. The present case has been presented in order again to draw attention to the occurrence of papilledema in the syndrome, with the hope that closer observation will bring to light further instances of choked disk in this syndrome. It is highly unlikely that an adequate understanding of this phenomenon will be arrived at until additional cases are carefully reported and analyzed. Perhaps even then, until the basic etiologic and pathologic factors are elucidated, no true understanding of the optic-nerve changes will be arrived at.

SUMMARY

A review of the available literature resulted in the finding of only nine documented cases of papilledema in the Guillain-Barré syndrome. A tenth case is here reported. After a brief consideration of the generally accepted hypotheses of the mechanism of the production of papilledema, the authors conclude that the papilledema of the Guillain-Barré syndrome cannot at present be adequately explained. A plea for more careful observation and reporting of papilledema in the Guillain-Barré syndrome is made.

31. Lichtenstein, B. W.: Textbook of Neuropathology, Philadelphia, W. B. Saunders Company, 1949, p. 99.

HEMIPLEGIA AND THROMBOSIS OF THE INTERNAL CAROTID SYSTEM

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CLINICAL recognition of thrombosis of the carotid vessels has opened a new field, which is increasing in importance. From early times this condition has been described as a rare finding at autopsy. It should now be recognized as a reasonably clear-cut clinical entity. Consequently, a series of cases is described and the differential diagnosis discussed.

The clinical recognition of this condition has been made possible by angiography, and it was in 1937 that Egas Moniz called attention to the angiographic appearance. In the same year blockage of the internal carotid artery was observed and reported by one of us (A. R. E.)[1] at the meeting of the Association for Research in Nervous and Mental Diseases in New York, using repeated injections of thorotrast® by the open technique.

More cases have been collected over the years and subjected to analysis. As they form an important clinical entity, it was considered desirable to submit them in more detail than would otherwise be required, including encephalographic and electroencephalographic conclusions, and to compare these cases with the cases of thrombosis of peripheral branches of the internal carotid artery.

Hemiplegic patients are nowadays often referred to the neurosurgeon in the belief that their condition, in the absence of obvious disorders of the vascular system, must be due to an intracranial tumor. It is indeed little appreciated that lesions of the cerebral blood vessels, including the internal carotid arteries, may occur in the complete absence of any other discernible involvement of the vascular system. It is also not fully appreciated that thrombosis of the internal carotid artery does not mean necessarily that the patient will be hemiplegic on one side and blind on the other. Yet, since the original communication by Egas Moniz and associates,[2] an increasing number of papers have been concerned with the so-called carotid syndrome, and it seems that a causal relation between thrombosis of the internal carotid artery and the neurological syndrome has tacitly been agreed upon.

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1. Elvidge, A. R.: The Cerebral Vessels Studied by Angiography, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:110-149, 1938.

2. Egas Moniz; Almeida Lima, and de Lacerda, R.: Hémiplégies par thrombose de la carotide interne, Presse méd. **45**:977-980 (June 30) 1937.

Thrombosis of the carotid arteries has long been known to occur, and an accurate description of it was given in 1949 by von Haller [3] in the case of an aneurysm of the aorta with a thrombus proceeding from it into the left common and internal carotid arteries. However, thrombosis of the internal carotid artery remained practically in the field of necropsy findings, without much clinical correlation, until a method of visualizing the cerebral vessels in a living human subject was made possible by Egas Moniz, in 1927.[4] But it was not until 10 years later, in 1937, that Moniz and his co-workers [2] published the first clinical report of four cases of thrombosis of the internal carotid artery, in all of which the condition had been taken for a space-occupying lesion and diagnosed only by angiography. It is worthy of note that the roentgenograms were taken in a way to show the cerebral vessels only, untii on two occasions the external carotid artery alone was visualized. After this experience, Moniz had the neck included in the arteriograms and could demonstrate thrombosis of the internal carotid artery for the first time in a living subject.

In the same year, one of us (A. R. E.) demonstrated occlusion of the internal carotid artery.[1]

Two cases have been studied in which the technique of injection seemed to be fairly satisfactory but in spite of this the internal carotid artery filled only as far as the siphon. Moniz has reported this phenomenon in both tumor of the temporal lobe and tumor of the pituitary as a result of pressure upon the vessels. In our cases the phenomenon was unexplained in one instance (possibly a question of technique), but in a second patient in whom the artery could not be traced beyond the anterior clinoid process, the block was thought to be due to an occlusion of the artery as a result of an old vascular lesion. The patient had complete hemiplegia and a diffuse cerebral atrophy of this hemisphere. The test was repeated but this time with complete failure to fill even the internal carotid loop itself. The external carotid circulation was well marked on the first plate in each instance. Upon the opposite right side, the arteriogram showed a well marked anterior cerebral artery, and indeed a posterior cerebral artery but the middle cerebral did not appear, which is unusual.

The most important clinical contributions have been, perhaps, the paper by Andrell,[5] who, in giving an account of nine personal cases, had found 23 in the literature up to 1943, and the papers by Krayenbühl and Weber,[6] in 1944, and Krayenbühl,[7] in 1945, who reported a personal series of 25 cases of cerebral thromboangiitis obliterans, 18 of which were concerned with thrombosis of the

3. von Haller, A.: De aortae venaeque cavae gravioribus, Göttingen, 1749; cited by Frøvig, A.: Bilateral Obliteration of the Common Carotid Artery: Thromboangiitis Obliterans, Acta psychiat. et neurol., Supp. 39, 1946.

4. Egas Moniz, L'encéphalographie artérielle, son importance dans la localisation des tumeurs cérébrales, Rev. neurol. **2**:72-90 (July) 1927.

5. Andrell, O.: Thrombosis of the Internal Carotid Artery, A Clinical Study of Nine Cases Diagnosed by Arteriography, Acta med. scandinav. **114**:336-372, 1943.

6. Krayenbühl, H., and Weber, G.: Die Thrombose der Arteria carotis interna und ihre Beziehung zur Endangiitis obliterans v. Winiwarter-Buerger, Helvet. med. acta **11**:289-333 (April) 1944.

7. Krayenbühl, H.: Zur Diagnostik und chirurgischen Therapie der zerebralen Erscheinungen bei der Endangiitis obliterans v. Winiwarter-Buerger, Schweiz. med. Wchnschr. **75**:1025-1029 (Nov. 24) 1945.

internal carotid artery. In America, attention has been called to the subject by Hyland,[8] Elvidge,[1] King and Langworthy,[9] Govons and Grant,[10] and others.

An analysis of 10 cases follows. A diagnosis of thrombosis of the internal carotid artery was made in six cases [11] and of the middle cerebral branches in four cases.[12] The findings in the two groups are compared. It is the purpose of this paper to review the clinical facts and to determine whether it is justifiable to speak of a "syndrome of thrombosis of the internal carotid artery," and to record the value of angiography in the study of cerebral thrombosis.

I. THROMBOSIS OF THE INTERNAL CAROTID ARTERY

1. Report of Cases

Case 1.—*Transient right hemiplegia at ages of 20, 23, 30 and 35 years, respectively, the last attack being followed by residual weakness in the right arm; transient defective speech, and recurrent convulsive seizures. Arteriogram: on left side, occlusion of internal carotid artery at entrance of carotid canal; failure of vessels to fill in repeat arteriogram; on right side, failure of middle cerebral artery only to fill.*

R. B., aged 40, was well until his 20th year, when he was seized with a stroke which left him temporarily paralyzed in the right arm and leg and the right side of the face. Partial recovery took place over a period of 10 days. A second episode, occurring when the patient was 23, lasted about one hour. A third, milder attack at the age of 30 involved the face and speech but lasted only a matter of minutes. At the age of 35, the patient suffered his most serious attack, which left him paralyzed in the right arm, the right leg, and the right side of the face and aphasic for three weeks. Recovery from this attack was much less complete than from the previous episodes, and the right arm has been practically useless ever since. There remains permanent facial weakness, and speech has been hesitating and slow. After one month he was able to get up and walk but could never resume his work. Four days after this attack the patient had his first epileptic attack. He was seized with a severe headache; the right side became spastic, and there was loss of consciousness for half an hour, followed by sleep and headache for three or four hours. The patient has had one or two similar seizures every month.

Personal and Family History.—The patient had a primary chancre at the age of 33 and received extensive antisyphilitic treatment. His parents and five siblings were alive and well.

Examination (July 13, 1937).—The patient was a well-developed white man, intelligent, oriented, cheerful, and cooperative. Olfaction was diminished on the left side. The ocular fundi were normal. The pupils reacted briskly to light and in accommodation. Fine nystagmic movements were present on gazing to the right, and slight weakness of the right lower part of the face was recorded. There was a spastic type of hemiparesis on the right side, more marked in the upper limb, with increase in deep reflexes and a Babinski reflex on the right.

The blood pressure was 110 systolic and 75 diastolic. Wassermann tests of the blood and spinal fluid gave negative reactions on two occasions. The total protein content of the cerebrospinal fluid was 29 mg. per 100 cc.; the Pandy reaction was negative; a count showed 19 lymphocytes per cubic millimeter. The cerebrospinal fluid pressure was not elevated. Roentgenograms of the skull revealed no important abnormality.

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8. Hyland, H. H.: Thrombosis of Intracranial Arteries, Arch. Neurol. & Psychiat. **30**:342-356 (Aug.) 1933.

9. King, A. B., and Langworthy, O. R.: Neurologic Symptoms Following Extensive Occlusion of the Common or Internal Carotid Artery, Arch. Neurol. & Psychiat. **46**:835-842 (Nov.) 1941.

10. Govons, S. R., and Grant, F. C.: Arteriographic Visualization of Cerebrovascular Lesions, Arch. Neurol. & Psychiat. **55**:600-618 (June) 1946.

11. Two more cases are recorded under "Addendum."

12. One more case is recorded under "Addendum."

An encephalogram demonstrated enlargement of both lateral ventricles, especially the left. The septum pellucidum lay 5 mm. to the left of the midline. Numerous dilated subarachnoid spaces overlay the cortex of the left hemisphere, and a few dilated spaces were seen over the right parietal region (Fig. 1*A*).

An arteriogram (July 29, 1937) of the left carotid system obtained with thorotrast® revealed partial occlusion of the carotid vessel at the carotid canal and complete stoppage at the anterior clinoid process (Fig. 1*B*). The branches of the external carotid artery were well shown. A second attempt to demonstrate the cerebral arteries also failed.

An arteriogram of the right side obtained with thorotrast® gave an interesting partial visualization. The anterior and the posterior cerebral arteries were seen but only the beginning of the middle cerebral artery was visible. The external carotid branches were visualized.

The reason for the failure of the right middle cerebral artery to fill is not quite clear. Because of the filling of both the anterior and the posterior cerebral arteries, in addition to the evidence of disease found on the arteriogram of the left side, it is probable that thrombosis of that vessel was the cause, despite the fact that no clinical signs pointed to involvement of the corresponding brain area.

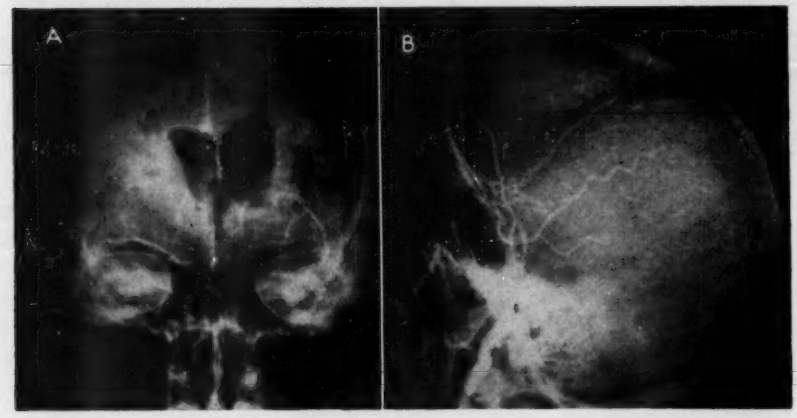

Fig. 1 (Case 1).—*A*, dilatation of both lateral ventricles, more pronounced on left side; shift of septum pellucidum 5 mm. to left; prominent subarachnoid spaces over left frontal pole. *B*, block of left internal carotid artery at level of anterior clinoid process.

CASE 2.—*Headache of two-years' duration; right hemiparesis and difficulty in concentration associated with poor memory for six months. Arteriogram: thrombosis of left internal carotid artery.*

C. P., aged 38, had complained of headaches for two years. The onset was gradual, and they first occurred in the right temporal region. For six months they had been persistent in the right temporal or in the left occipital region. Never severe, they usually came on after meals; they did not interfere with sleep. The headaches were increased by straining or bending. He had had occasional double vision and difficulty in focusing his eyes. He complained of ringing in the right ear and of smelling peculiar odors. He had had weakness of the right side of the mouth for six months and pain in the left eye for two months; the latter had been increasing in severity. For six months the patient had been unable to concentrate on his work as a grocer and had had some difficulty with his memory.

Family and Personal History.—The patient had had no illnesses other than the usual childhood diseases and no serious accident. Tonsillectomy and adenoidectomy had been performed when he was 33. His father died at the age of 65, of pneumonia; his mother is living and well. Six siblings are alive and in good health; four siblings died in infancy.

Examination (June 22, 1941).—Examination showed a well-developed and well-nourished white man, who did not appear to be in acute distress. The blood pressure was 105 systolic and 75 diastolic. The urine was normal, and the hemogram was normal except for leucopenia (4,500 white blood cells), and the blood plasma showed low refraction. Roentgenograms of the skull showed no abnormality. The cerebrospinal fluid was under normal pressure; the protein measured 27 mg. per cubic centimeter; the Lange colloid gold curve was 0012210000, and the Wassermann reaction was negative.

The patient was rational, cooperative, and well oriented. However, he did not appear to be certain in answering questions, nor was he able to concentrate very well. There was no objective disturbance of olfaction. The optic disks were normal. Visual acuity was 20/40 in each eye; the visual fields were full on tangent-screen examination and the pupillary reactions were normal. Hyperesthesia to pinprick was reported over the left side of the face. Corneal reflexes were present and equal on the two sides. There was weakness of the right side of the face and of the right arm and hand. The biceps and triceps reflexes were brisker on the right side than on the left; the knee and ankle jerks were symmetrically brisk. The abdominal reflex was absent, and a Babinski reflex was elicited on the right. There was

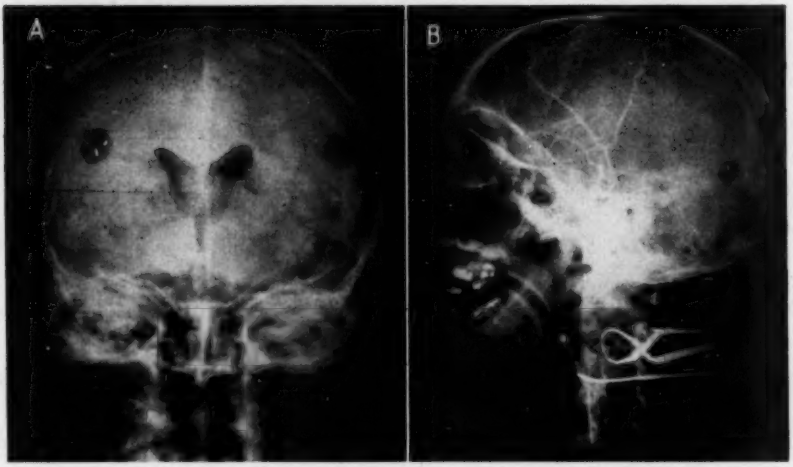

Fig. 2 (Case 2).—*A*, slight relative dilatation of left lateral ventricle. *B*, left internal carotid artery, represented by short, narrow stump.

some loss of two-point discrimination over the right hand and, to a less degree, over the right foot.

Ventriculogram (June 26): The lateral ventricles showed slight dilatation, portions 2 and 3 on the left side being slightly larger than those on the right side, and dilatation of the subarachnoid spaces over the anterior portion of the frontal lobes (Fig. 2*A*).

Electroencephalogram (July 4): Delta waves with frequencies of 2 and 6 cps appeared to arise deep to the left temporal or frontotemporal region, with surface cortical localization vague and with considerable transmission to the homologous region of the right hemisphere.

During hospitalization, the patient had several spells of transient blindness of the left eye. The ophthalmoscopic examination revealed constriction of veins and arteries and some segmentation of the arteries.

Arteriogram with Thorotrast® (July 21): The left external carotid artery was unusually small. The internal carotid artery appeared slightly smaller than normal, had a bluish cast, and was obviously the site of a thrombus. The firm portion of the thrombus, on palpation, was at the bifurcation of the common carotid artery or just distal to it. When the internal carotid artery was pricked about 2 cm. distal to the bifurcation, some blood came back, which

was semisolid in consistency. It continued to ooze two or three small drops, and the bleeding ceased with packing. It was impossible, therefore, to inject thorotrast® into this vessel, and the arteriographic study was carried out, utilizing the left external carotid artery at a similar point, about 2 cm. distal to the bifurcation. The x-ray films showed a patent external carotid artery with its branches. The internal carotid artery was represented by a short, narrow stump (Fig. 2*B*). The patient was discharged on Aug. 2, unimproved.

CASE 3.—*Spells of aphasia and weakness of right hand "for some years"; headaches for over a year. Within 24 hours, onset of right hemiplegia and total aphasia. Arteriogram: occlusion of left internal carotid artery in its proximal portion.*

Sister Marie D., aged 25, had complained of headache for over a year. In February, 1942, when signing a check, she found that she was unable to write with her right hand. This paresis was only momentary. On April 23, 1943, when preparing the altar, she apparently was unable to distinguish the flowers, as indicated by the manner in which she arranged them. On April 29 she said she felt unwell and asked to be allowed to go to bed. She stayed in bed

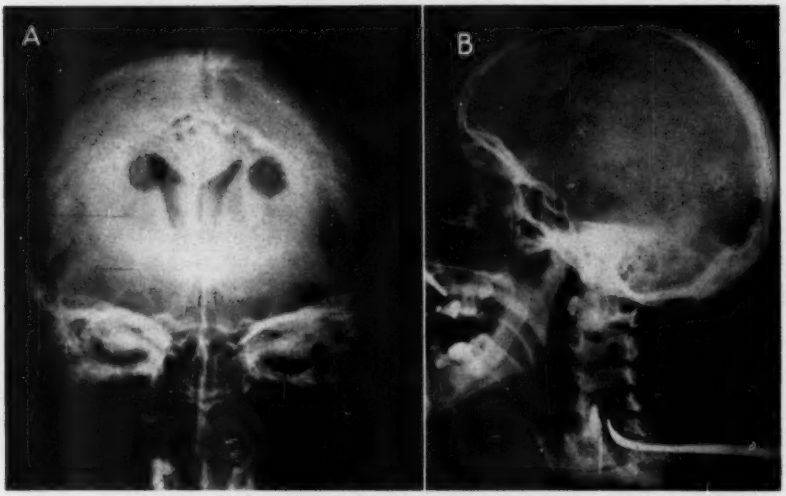

Fig. 3 (Case 3).—*A*, slight shift of ventricular system to the right; no local deformity, and little significant asymmetry. *B*, typical cone-shaped stump of thrombosed internal carotid artery just distal to bifurcation of common carotid artery (external carotid artery was closed during the injection).

for 15 minutes, then got up, and said that she did not know what she was saying when she asked to go to bed. About the same day she complained of a pain in the right eye and cheek. About 10 a. m. on May 1 the patient was found fumbling at the bathroom, with her clothes awry. She was helped to the infirmary and seemed unsteady on her feet. Later she began to talk nonsense. In the afternoon she appeared unable to speak and could answer only "yes" and "no" to all questions. She apparently was able to understand what was said to her. Later in the day she was seen by a physician, who said that her whole right side was paralyzed. On May 1 and 2, she was unable to swallow, and her tongue appeared to deviate to one side. From May 1 the patient remained fully conscious. She was able to recognize her friends and appeared to understand fully what was said to her. There was some return of strength in the right arm and leg, but speech did not improve. It appeared that during the preceding few years the patient had had spells of aphasia with weakness in the right hand, lasting several hours, the attacks occurring about once a month.

Family History.—Two uncles on the father's side were insane, and the patient's sister was nervous.

Examination (May 4).—The patient lay flat in bed in no acute distress. She was unable to speak but was fully conscious and could understand what was said to her. Nothing of note was found on general physical examination. The blood pressure was 130 systolic and 90 diastolic. The Kahn test of the blood gave a negative reaction.

The patient was cooperative. She was able to say "yes" and "no" only. When she did speak, it was only in a whisper, and she appeared to be unable to raise her voice. She appeared to understand but sometimes gave wrong answers. She recognized objects, could write her name with the left hand, and understood how to use various objects. The optic disks were sharply defined and of good color. The visual fields appeared normal on confrontation tests. There appeared to be impaired sensation to pinprick over the maxillary distribution of the right trigeminal nerve. There were obvious weakness of the right side of the face and some impairment of sensation for sweet and salt on the left side of the tongue. There were deviation of the uvula to the right, absence of the gag reflex, and almost complete aphonia. The tongue was in the midline but could not be protruded. There were complete paralysis of the right arm and weakness of the right lower limb. The biceps and triceps jerks were brisker on the right than on the left. The abdominal reflex was not obtained on the right. The plantar reflexes were flexor.

Ventriculogram (May 4): There was a shift of the septum pellucidum of 4 mm. to the right. The lateral ventricles were comparatively small and presented little asymmetry. The third ventricle showed a slight shift to the right (Fig. 3*A*).

Electroencephalogram (May 8): Continuous random delta waves of a frequency of 1 to 4 cps and others of large amplitude and a frequency of 1 to 2 cps were reported, with maximal activity in the left frontotemporal region, suggesting an acute degenerative lesion.

Arteriogram (May 13): A silk ribbon was placed beneath the left common carotid artery and a strand of white braided silk about the external carotid and superior thyroid arteries. A total dose of 25 cc. of thorotrast® was injected in two amounts for routine stereoscopic lateral roentgenograms. During each injection the external carotid artery and the superior thyroid branch were occluded by traction. The carotid arteries were small. On palpation, there was absence of pulsation in the internal carotid artery distal to the bifurcation, whereas there was a good pulsation of the common carotid artery. The roentgenograms showed that none of the injected material had passed distally more than 1.8 cm. beyond the point of the injecting needle (Fig. 3*B*).

During hospitalization the patient showed slight improvement of the movements of the fingers, hand, and leg on the right side. There was no improvement in the aphasia.

CASE 4.—*Fainting spells every three or four days during three-month period two years before; since then violent pulsating frontal headaches. Right hemiplegia and aphasia of sudden onset one week previous to admission. Arteriogram: thrombosis of left internal carotid artery close to apex of the petrous portion of temporal bone.*

A. M., aged 33, a workman employed in a garage, began to complain during the winter months of 1944 of violent right frontal pulsating headache, occurring at any time during the day, lasting more than one hour, and not relieved by acetylsalicylic acid. There was no vomiting, stiffness of the neck, or visual disturbance. Three weeks after the onset, he fainted on getting out of bed one night to go to the bathroom. His wife heard him fall and found him unconscious on the floor. He did not appear to be in a convulsive state and was revived by cold compresses. He did not recall having had any aura. He continued to the bathroom and walked back to bed, complaining of general weakness. The next day the physician made the diagnosis of angina pectoris. His headaches became progressively more painful and occurred about twice a week. A second fainting spell occurred at home, one week after the first one, while the patient was sitting and reading. His wife saw him fall backward against his chair in silence. There was no convulsive movement and no cry. Again, he was easily revived by cold compresses. These attacks occurred every two to three days for three months and then ceased until one week before his admission, at which time he became hemiplegic on the right side and aphasic. During 1945 he had noticed round, dark-blue spots, 0.15 in. (4 mm.) in diameter, which appeared on the dorsal surface of both feet, on his forearms, and over the

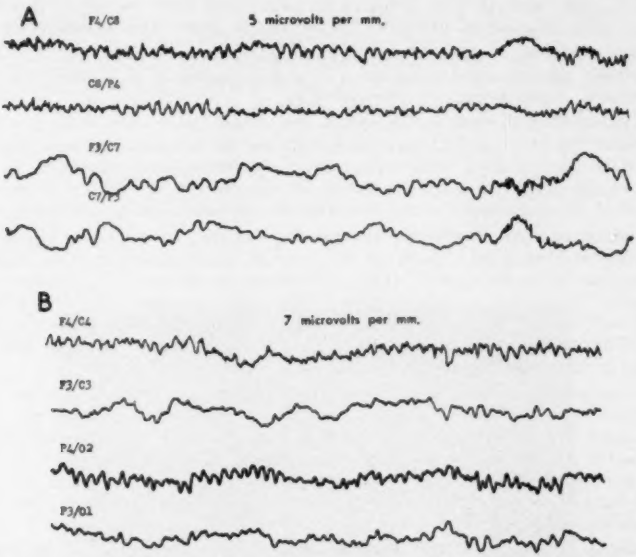

Fig. 4 (Case 4).—*A*, abnormal slow waves in left frontotemporoparietal region (two lower lines). *B*, disturbance of alpha rhythm in left parieto-occipital region (fourth line), as compared with normal recording from right side (third line).

Fig. 5 (Case 4).—Narrowing of left internal carotid artery within carotid canal and arrest of dye at foramen lacerum.

trunk. These spots, at first blue, would turn red in two days, become painful, and finally fade. On July 17, 1946, while at home sitting at the table before lunch, the patient dropped a cup which he was holding and fell backward. He suffered immediate right hemiplegia and aphasia.

Personal and Family History.—The patient had undergone an operation for bilateral inguinal hernia in 1937. His father died at the age of 78, and his mother, at 60, of tabes. Two brothers died in infancy. Eight siblings are alive and well.

Examination (July 27, 1946).—The patient was an alert white man, whose general status was normal. The blood pressure was 110 systolic and 80 diastolic. The urine was normal, and the Kahn reaction of the blood was negative. The Wassermann reaction of the cerebrospinal fluid was negative; proteins measured 86 mg. per 100 cc., and the Pandy reaction was negative. Roentgenograms of the skull and chest revealed nothing pathological.

The patient was alert and cheerful; he showed almost complete motor and sensory aphasia. Visual acuity and visual fields could not be accurately tested on account of the aphasia, but both seemed to be greatly impaired. The optic disks appeared clear. The pupillary reactions were normal. There was a slow spontaneous horizontal nystagmus. The corneal reflex on the right was absent. There was pronounced paresis of the right side of the face, and the tongue deviated to the right on protrusion. He had complete right hemiplegia with absence of the abdominal reflexes and a Babinski sign on the right.

Electroencephalogram (July 30): The electroencephalogram revealed a source of delta wave activity which occurred maximally in the left temporal region but was seen over the frontal, central, and parietal regions on the left side, with relative loss of alpha rhythm from the left parieto-occipital region, indicating interruption of the optic radiations on the left side. The low-to-moderate amplitude and extreme slowness in frequency (from ½ to 2 cps) of the delta activity suggested that the lesion was acute and severe. An intracerebral lesion of the hemisphere was suggested (Fig. 4).

Ventriculogram (Aug. 1): The ventriculogram showed slight atrophy of the left hemisphere, more pronounced anteriorly than elsewhere, with some question of a small porencephaly communicating with the anteroinferior portion of the first part of the left lateral ventricle.

Arteriogram (Aug. 8): The internal carotid artery was relatively large; a total dose of 24 cc. of thorotrast® was injected in two amounts into the internal carotid artery while a temporary ligature of the external carotid artery was pulled upon so as to cause occlusion of this vessel. The cervical portion of the internal carotid artery was well filled. The diameter of the artery tapered within the carotid canal until at the petrous tip the column of dye in the artery was so thin that it could no longer be seen (Fig. 5).

CASE 5.—*Personality change and poor memory for three or four months. Sensations of numbness in right hand, followed 10 days later by onset within five days of complete right hemiplegia with aphasia. Arteriogram: thrombosis of left internal carotid artery.*

Mrs. F. C., aged 48, had shown a change of personality during the previous three to four months. She cried upon the slightest excitement. She had to write things to be done; otherwise she would forget them. During the first days of March, 1948, the patient complained on several occasions that her right hand was becoming numb, and she would rub it with her left hand. On the evening of March 10 she complained of numbness in her right leg while sitting after dinner. She noticed difficulty in standing and walking. She did not have proper control of her leg. On awakening the next day she found that her right leg was entirely paralyzed. The right arm became involved on the following day. On March 13 the patient was admitted to the hospital. On March 14 she suddenly lost her speech but seemed to understand what was said. She had had no headache, nausea, or dizziness. Her appetite remained excellent. She continued to be mentally alert and did not show any disturbance of speech until the sudden onset of aphasia on March 14.

Personal and Family History.—Many years before, the patient had had a mastoidectomy, an appendectomy, a hysterectomy, and an ovariectomy. Three months before admission the patient had been rendered unconscious for 30 minutes by a high concentration of illuminating cooking gas. She was cyanotic at the time and remained drowsy for 24 hours. Her parents died when very old, of an unknown cause. Two sisters died in infancy; 12 siblings are alive and in good health.

Examination.—The patient was a stout woman who, aside from her present condition, did not seem to be in acute or general distress. There were no signs of cardiorespiratory embarrassment. The blood pressure was 140 systolic and 90 diastolic. The carotid pulsation was perhaps slightly weaker on the left. There were good pulsation in the dorsalis pedis and the femoral artery, less obvious pulsation of the posterior tibialis artery, and no pulsation of the popliteal artery on either side. Oscillometric readings (maximum) are tabulated as follows:

	Right	Left
Above knee	0.5	1.0
Below knee	0.75	1.5
Above ankle	1.0	1.25
Dorsalis pedis artery	0.0	Faint flicker

The urine was normal. The Kahn reaction of the blood was negative, and the cerebrospinal fluid was normal. A hemogram showed slight normocytic, hypochromic anemia, moderate

Fig. 6 (Case 5).—Dilatation of both lateral ventricles, more pronounced on left side; shift of septum pellucidum 2 mm. toward right.

leucocytosis with neutrophilia, and moderate lymphocytosis. The sedimentation rate was moderately increased (20 mm. in the first hour). Roentgenograms of the skull and of the abdomen showed no abnormality. Roentgenograms of the chest showed no evidence of recent intrathoracic disease. The cardiac shadow did not appear to be abnormally large.

The patient was alert and cooperative and resented her inability to speak. She proved to be well oriented for time, space, and herself. Her speech consisted mainly in "yes" and "no"; however, she could name a few objects properly, articulating the words very slowly. There was also some apraxia; she had difficulty in protruding the tongue, although she could move it and understand the command. Sense of smell was intact on both sides. The optic disks appeared normal. Vision was 4/5 in the right eye and 4/6 in the left eye. Careful confrontation tests revealed no field defect. The pupillary reactions were normal. There was conspicuous paralysis of the lower right side of the face. There were complete loss of power in the right upper limb and severe paralysis of the right lower limb. Examination revealed

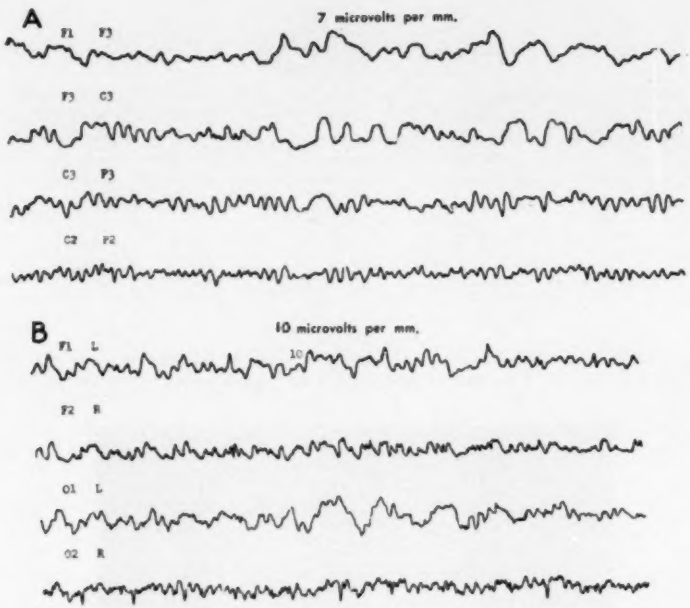

Fig. 7 (Case 5).—*A*, continuous abnormal slow waves over left frontotemporal region (first and second lines); random slow waves over left temporoparietal region (third line); normal activity on right side (fourth line). *B*, continuous abnormal slow waves over left inferior frontotemporoparietal region (first and third lines).

Fig. 8 (Case 5).—Blunted stump of left internal carotid artery shown distal to bifurcation of common carotid artery. The artery again appears as it leaves the carotid canal to enter the cranial chamber as a narrow vessel, which increases in size. The artery regains its normal caliber beneath the anterior clinoid process.

the hyperreflexia on the right side, with ankle clonus and a Babinski reflex, and probable impairment of position sense and two-point discrimination in the fingers of the right hand.

Pneumoencephalogram (March 22, 1948): Both ventricles were larger than normal, the left being greater than the right. The floor of the body of the left ventricle lay lower than that of the right ventricle. The subarachnoid markings were wide and deep and were seen mostly on the right side (Fig. 6). The septum pellucidum was shifted 2 mm. to the right.

Electroencephalogram (March 24, 1948): There were random slow waves, with a frequency of 2 to 5 per second, which were maximal from the frontotemporal regions and showed phase reversals in the lower frontal region. The abnormality was occasionally rhythmic at 2 cps in the left frontotemporal region, and there was some rhythmic 6 cps activity in the central regions. Normal alpha activity was obtained from the left parieto-occipital region. The right hemisphere showed little abnormality. The electroencephalogram suggested a generalized abnormality over the left hemisphere, with the most pronounced abnormality in the left inferior frontal region (Fig. 7).

Arteriogram (March 25, 1948): The bifurcation of the left common carotid artery appeared normal, and pulsations were present. No attempt was made to isolate the external carotid artery. A total dose of 22 cc. of thorotrast® was injected in two amounts, for stereoangiograms, into the common carotid artery about 2 cm. proximal to the bifurcation. An excellent demonstration of the external carotid artery and its branches was obtained, but only the proximal, blunted stump of the internal carotid artery was filled. The artery was again visualized as a thread, rapidly increasing in size, as it left the carotid canal to pass through the wall of the cavernous sinus. As the artery made its loop beneath the anterior clinoid process, it regained its normal caliber and gave off a normal ophthalmic branch. Beyond the anterior clinoid process the diameter of the artery again diminished, and about 8 mm. above it there seemed to be a filling defect. Some at least of the middle cerebral branches had filled with thorotrast® to their smallest twigs. No anterior cerebral artery was visualized (Fig. 8).

While the patient was in the hospital, her speech improved. Articulating slowly, she was able to make simple sentences. There was some improvement in the power of the right leg. She was discharged on March 31, 1948.

CASE 6.—*Vague visual complaints for four months previous to a "stroke" which left the patient hemiplegic on the right side and aphasic. Good recovery of motor function; no recovery of the aphasia. Arteriogram three months after stroke: thrombosis of left internal carotid artery.*

A. G., aged 50, had complained of increasing visual disturbances since August, 1947. He soon complained of double vision and general fatigue, and his wife observed that he slept more heavily. He continued, however, to work full time as a truck driver and did not want to go to a doctor. On Dec. 22, 1947, he went to work as usual but was brought home about half an hour later unconscious. While bending to pick up something, he had slumped over. On regaining consciousness three-quarters of an hour later, the patient was hemiplegic on the right and completely aphasic. He was taken to a hospital, where roentgenograms of the skull, tests of the blood and spinal fluid, urinalysis, and examination of the fundi showed nothing abnormal. The patient was referred to another clinic, where the diagnosis of disseminated sclerosis was made, with brain tumor as a possibility. A pneumoencephalogram was obtained on Feb. 16, 1948. The lateral and third ventricles were greatly dilated. The cerebrospinal fluid showed 28 mg. of total protein per 100 cc. and a normal cell count. Gradual partial recovery of the hemiplegia took place.

Personal and Family History.—The patient had had typhoid in 1924. He was a heavy smoker and drank for many years an average of four to five bottles of beer a day. His father died at the age of 81, suddenly; his mother died at 48, of pulmonary tuberculosis. One brother died of cancer; four siblings are alive and in good health. Two children are suffering from the after-effects of poliomyelitis.

Examination (May 14, 1948).—The nutritional and general condition was excellent. Two small fibromas were present on the left side of the face; one, the size of a walnut, was observed in the right occipital region. The blood pressure was 135 systolic and 90 diastolic. High up in the neck, the left carotid artery pulsated less than the right. The pulse of the right dorsalis pedis artery was weaker than that of the left. The radial, temporal and occipital

arteries pulsated normally. The urine was normal, and the Wassermann reaction of the blood was negative. The patient had a severe sensorimotor aphasia. He could say "yes" and "no" but could not read or write. The optic disks were normal in appearance, and the arteries appeared to be narrow on the left side. Some degree of homonymous hemianopsia was thought

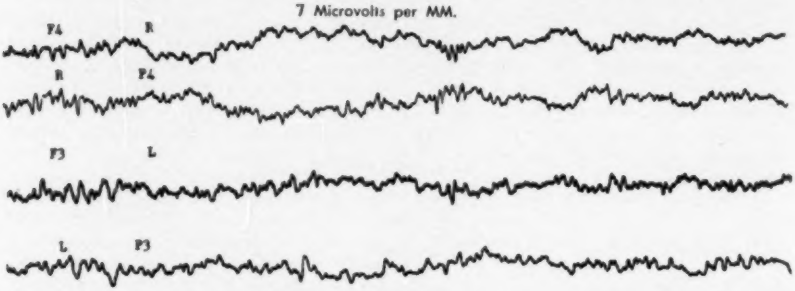

Fig. 9 (Case 6).—Poorly regulated background activity of low voltage bilaterally with diffuse slow waves.

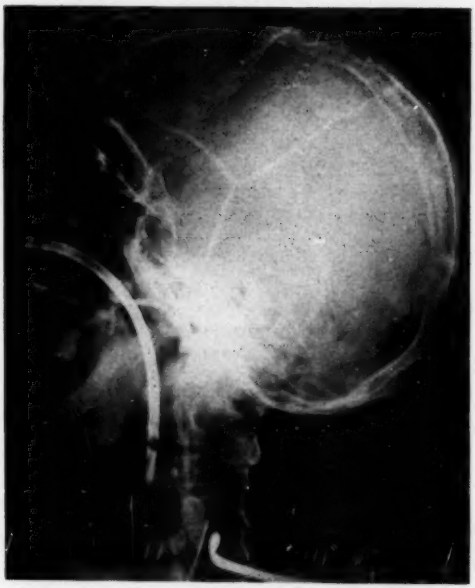

Fig. 10 (Case 6).—Occlusion of left internal carotid artery extending from bifurcation of common carotid artery.

to be present on the right. Pupillary reactions were normal. There was questionable weakness of the right lower part of the face. Though there was no gross motor loss, fine movements were less well performed with the right hand than with the left. Tendon jerks were slightly brisker in the right arm than in the left. The plantar reflexes were of flexor type bilaterally. There was definite impairment for sense of position, and probably for two-point discrimination, in the fingers of the right hand. Roentgenograms of the skull showed the pineal gland to lie

2 mm. to the left of the midline. The glomi of the choroid plexuses of the lateral ventricles showed calcification. A roentgenogram of the chest showed a normal condition. Roentgenograms of the abdominal aorta and of the legs showed slight deposits of calcium in the arteries.

Electroencephalogram (May 15, 1948): There was irregularity of alpha rhythm. Slow waves were present diffusely over the frontotemporal region principally, with occasionally a maximum over the left inferior temporal region. Similar irregular low-voltage, slow-wave activity was recorded from the pharyngeal electrode at the base (Fig. 9).

Arteriogram with thorotrast® (May 22, 1948): The left common carotid artery was somewhat thickened. In no instance was the internal carotid artery visualized, in spite of several attempts at filling. Blockage occurred at the bifurcation of the common carotid artery. (Fig. 10).

2. Clinical Analysis

Incidence.—The frequency with which occlusion of the internal carotid artery occurs can be estimated only roughly. This is due to the fact that reports of such cases published in the world literature are not taken from comparable material. Hultquist,[13] among 1,300 nonselected autopsies, reported 38 cases of large thromboemboli, 20 microscopic thromboemboli, and 15 questionable microscopic ones. Chiari [14] reported seven cases of thrombosis of the carotid artery among 400 autopsies. Krayenbühl and Weber [6] found nine cases among 1,451 autopsies performed in the Pathological Institute of Zurich during 1940.

Moniz and associates [2] found four cases among 500 patients on whom angiographic procedures had been performed in an attempt to localize a suspected neoplasm of the brain. Our six cases were obtained from a series of about 150 arteriograms. The great difference between the 0.8% of Moniz' first report and our 4% is readily understandable, since Moniz was working with patients who were suspected of having brain tumors, whereas our patients studied arteriographically were mainly those in whom vascular lesions were suspected clinically.

The age incidence varied considerably. At the time of their first symptoms our patients were from 20 to 50 years of age; the ages of Andrell's [5] patients were from 24 to 60 years, and Krayenbühl and Weber's,[6] from 15 to 59. As will be seen later, thrombosis of the main branches of the carotid artery has been reported in children.

The sex incidence shows that men are more frequently affected than women, the ratio being 4:2 in our series, 7:2 in the series of Andrell,[5] and 24:10 in the series of Krayenbühl and Weber.[6]

As far as race is concerned, cases have been reported among the Chinese population and the American Negroes.

Worthy of note may be the fact that in all our cases the left carotid artery was involved. Larger collected series from the Swiss and Swedish literature show an average proportion of 2:3 of occlusion on the left side.

Mode of Onset and Evolution.—From the study of the literature and of our own cases, we have found that the patients may be grouped into two categories. In the first group, the patients give a history of transient and recurrent episodes of similar pattern, but, as a rule, less severe than those for which the patient is finally referred to the specialist. Thus, recurring disturbances of a hemiplegic nature

13. Hultquist, G.: Über Thrombose und Embolie der Arteria carotis und hierbei vorkommande Gehirnveränderungen, Jena, Gustav Fisher, 1942; cited by Krayenbühl and Weber.[6]

14. Chiari, cited by Krayenbühl and Weber.[6]

result eventually in a more or less complete hemiplegia, with or without aphasia (Cases 1 and 3). Between recurrent episodes the patient may be in good health.

The second group comprises patients in whom the onset of the hemiplegic syndrome, with or without aphasia, has not been preceded by disorders of the same pattern. Patients give a history of prodromal symptoms without localizing value, such as fatigability, headaches, blurring of vision, and impairment of memory and concentration. The onset of the hemiplegia is apoplectic (Cases 4 and 6) or progressive (Cases 2 and 5). At times the apoplectic onset may be associated with loss of consciousness, as in Case 6.

Thrombosis of the internal carotid artery seems thus to lead sooner or later to hemiplegia, which may be associated with impairment of visión or hemianoptic disturbances and, if on the dominant side, with aphasia. In each case, however, the condition seems to progress in its own way. The mode of onset, whether progressive or apoplectic, and the previous evolution, whether characterized by recurrent episodes of the same pattern or by vague complaints, are, in our experience, of little help in foreseeing the future course of the patient's illness.

Symptoms and Signs.—That thrombosis of the internal carotid artery may not be associated with any clinical, objective abnormal neurological signs has been illustrated again recently by the case of Govons and Grant.[10] The man, aged 24, had suffered from epileptiform seizures (unconsciousness, rigidity, biting of the tongue, and postictal amnesia and confusion, with no movements of the extremities) since childhood and had shown no objective neurological signs. It has been shown in the preceding paragraph, however, that the characteristic and commonest feature presented by the patient with thrombosis of the internal carotid artery is a contralateral hemiplegic syndrome. There are other features, and they may be grouped conveniently into disturbances of the motor, sensory, and coordinating systems, of the special senses, of the mental state, and of non-nervous origin.

Motor Disorders: These vary greatly, from a slight drooping of one corner of the mouth, perhaps associated with impairment of discrete movements of the fingers (Cases 2 and 6) to a massive hemiparesis (Cases 3, 4, and 5). The hemiparesis following an apoplectic onset may be transitorily of the flaccid type; otherwise spasticity with hyperreflexia is the rule. It is a common observation in cases of thrombosis of the internal carotid artery that the upper limb is more affected than the lower. Recovery from complete hemiplegia, as in Cases 5 and 6, begins in the leg but leaves, even in favorable cases, residual weakness in the fingers, and in the lower part of the face at times a slow blinking reflex.

Among the motor cranial nerves, the involvement of the seventh has already been mentioned. Central involvement of the 12th cranial nerve was present in Case 4 and has been reported by Krayenbühl and Weber,[6] King and Langworthy,[9] Andrell,[5] and others. It probably occurs frequently as a transient sign after apoplectic or severe insults. Impairment of other motor nerves has not been encountered in our series; however, ptosis has been observed by Scheinker[15] and others.

Sensory Disorders: In contradistinction to the motor disturbances, which are practically always present, objective impairment of sensation of the discriminative

15. Scheinker, I. M.: Cerebral Thromboangiitis Obliterans and Its Relation to Periarteritis Nodosa, J. Neuropath. & Exper. Neurol. 4:77-87 (Jan.) 1945.

qualities is an inconstant finding. Often there is only slight impairment of cortical sensation (Cases 2 and 6). Patients may experience spells of numbness before the onset of physical signs in the limbs which are to become involved.

Disturbances of Special Senses and Remaining Cranial Nerves: Smell sensibility was diminished on the side of the lesion in our first case and was intact in the others. Hearing was not affected. Taste sense was found to be normal when it could be tested. Papilledema has been reported by Moniz [2] and Krayenbühl and Weber [6]; thrombosis of the central artery of the retina, by Hyland [8]; optic nerve atrophy, by King and Langworthy [9] and Hyland.[8] King and Langworthy [9] stated that severe impairment of vision, ending in blindness and associated with optic nerve atrophy on the side of the occluded carotid artery, is a characteristic feature of the "carotid hemiplegia." Our cases, however, as well as many others described in the literature, such as those reported by Andrell,[5] Krayenbühl and Weber,[6] Govons and Grant,[10] and others, show that this is far from being the rule. Impairment of vision of a hemianoptic type on the side opposite the lesion is not infrequently observed (Cases 4 and 6) but is by no means a common feature. In a survey of 38 cases, Milletti [16] found four cases of homonymous hemianopsia. Concentric constriction of the visual fields was considered by Chao and co-workers [17] as a "consistent symptom." We believe, however, that this finding is due to an impairment of the attention rather than to a lesion of the visual pathways. For Milletti, a diminution of 50% of the value of the systolic pressure of the central artery of the retina, with the diastolic value remaining about normal as compared with the opposite side, is a good sign of primary thrombosis of the internal carotid artery. Pupillary reactions were normal in our cases. Milletti stated that miosis on the side of the lesion is frequently encountered.

Mental State: Clinicopathological studies of thrombosis of cerebral arteries and the resulting brain softening usually indicate that there is marked deterioration of the patient's mental state. However, it is our experience that in relatively young patients in whom thrombosis has been diagnosed by angiography the mental condition is generally astonishingly good in the early stages as compared with the hemiplegic syndrome, which is often very severe. Even after a rapid, sometimes apoplectic, onset of hemiplegia associated with aphasia, the patients are surprisingly cooperative and well orientated; their memory is far less impaired than one would expect it to be; they show a live interest in their surroundings and are as active as possible, trying to compensate for their inability to speak by an expressive gesture. On the day of admission F. C. (Case 5), one week after the sudden onset of aphasia, was able to utter only a few words very slowly and with great difficulty. On the next morning, having "rehearsed hard for many hours" (as the roommates reported), the patient grasped the visiting physician's hand and said extremely slowly, "When will you be able to do something for me?" If the mental state is seriously altered, other factors, such as increased intracranial pressure, intoxication, infection, and generalized brain disease, may play a role. Contrasting sharply at times with the relative integrity of the general mental picture, the aphasia stands

16. Milletti, M.: Le diagnostic de la thrombose primitive de la carotide interne dans le région cervicale au moyen de la détermination des valeurs de la pression systolique de l'artère centrale de la rétine, Presse méd. **54**:655-656 (Oct. 5) 1946.

17. Chao, W. H.; Kwan, S. T.; Lyman, R. S., and Loucks, H. H.: Thrombosis of the Left Internal Carotid Artery, Arch. Surg. **37**:100-111 (July) 1938.

out as a prominent symptom. It is generally of the motor type, though combined sensory-motor involvement is frequent.

General Examination and Laboratory Data: The general condition of our patients was remarkably good. Particularly worthy of note was the absence of cardiac involvement in any of our patients and the normal blood pressure. Diminution or loss of carotid pulsation high up in the neck may be noted. This sign has been reported by Krayenbühl and Weber,[6] Chao and others,[17] Hyland,[8] and King and Langworthy.[9]

Routine examinations of the blood and urine revealed no abnormality in five cases, slight changes in the morphological blood picture being present in one case. Lumbar puncture was performed in five cases. The cerebrospinal fluid was under normal pressure. The protein content was normal in four cases. It was increased to 86 mg. per 100 cc. in Case 4. There were 19 lymphocytes per cubic millimeter of spinal fluid in Case 1, but the cell count was normal in the other cases.

Miscellaneous Disorders: Headaches, though not infrequent, were of no particular type or specific location. In Case 2 the patient had gradual onset of headache over a period of two years. In Case 4 the patient suffered from violent pulsating headaches in the right frontal region for two years before the onset of sudden hemiplegia of the right side. The headache was at first associated with fainting spells.

An infrequent feature is the occurrence of epileptic seizures, as in Case 1. Similar observations were made by Erickson,[18] Krayenbühl and Weber,[6] and Govons and Grant,[10] and Sorgo [19] said that convulsions were rare. Acute thrombosis of cerebral arteries is accompanied with convulsions in 8% of cases, according to Merritt and Aring.[20]

Electroencephalography.—Electroencephalograms were recorded for five patients and showed constantly, as the main feature, slow delta waves of varying amplitude, localized to the frontotemporal region of the involved side. The appearance of the delta waves suggested that there was a degenerative or destructive lesion in the area from which the action potentials were being recorded.

Roentgenography.—As a rule, patients with "carotid hemiplegia" present a normal x-ray picture of the skull. Although this is a negative feature, the point is of interest in making the differential diagnosis. Calcification of the pineal gland and of the glomi of the choroid plexuses may aid or confuse in differential diagnosis. In Case 6 the pineal body was shifted 2 mm. to the side of the lesion.

Films of the chest, abdomen, and limbs may show modifications of the heart or large vessels (Case 6, calcification of the abdominal aorta and of the large vessels of the limbs) which are helpful for etiological considerations. X-ray pictures of the base of the skull may be of use in cases of suspected congenital absence of the internal carotid artery, since they show the absence of the carotid canal through the petrous bone.

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18. Erickson, S.: Über Arteriographie bei Thrombose in der Carotis interna, Acta radiol. **24**:392-402, 1943.

19. Sorgo, W.: Über den durch Gefässprozesse bedingten Verschluss der Art. carotis interna, Zentralbl. f. Neurochir. **4**:161-179 (July) 1939.

20. Merritt, H. H., and Aring, C. D.: The Differential Diagnosis of Cerebral Vascular Lesions, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:682-695, 1938.

Pneumoencephalography.—Cases 1 to 5 were studied by means of pneumoencephalography in the Montreal Neurological Institute. In four cases, air studies showed enlargement of the lateral ventricle on the side of the lesion, the increase in size being more marked in the anterior portion. Ventricular study in Case 6, made elsewhere, showed bilateral ventricular enlargement. In Cases 1, 2, and 4 there was deepening of the subarachnoidal sulci in the frontal region. Shift of the septum pellucidum may occur as far as 5 mm. to one side or the other, depending on whether there was atrophy of long standing (Case 1) or whether edema was still present (Cases 3, 5, and 10, with edema of at least three to nine days' standing). Localized deformity of the ventricle, when it occurs, is not of the "cut-out" variety, but local dilatation of the ventricle indicates atrophy of the adjacent portion of the brain, as in Cases 1 and 5.[21]

The common pneumographic finding, as emphasized by Andrell,[5] Krayenbühl and Weber,[6] Moniz,[2] and Govons and Grant,[10] is dilatation of the whole lateral ventricle, or at least of the whole anterior horn, on the side of the occluded carotid artery. These findings correspond to a shrinkage of the involved cerebral substance, i. e., to a cerebral atrophy of a greater or less extent.

Cerebral Angiography.—In all the cases reported in this series arteriography was performed with thorotrast.® Stereoscopic lateral arteriograms and phlebograms were taken. It was found that the commonest site of thrombosis of the internal carotid artery was just distal to the bifurcation of the common carotid artery (Cases 2, 3, and 5; see also Cases 6 and 9). Other points of stoppage were at the anterior clinoid process and at the foramen lacerum.[22]

As emphasized by Krayenbühl and Weber,[6] the failure to visualize the dye in the vessel does not necessarily mean that the vessel is thrombosed. These authors consider that only a conical narrowing of the dye before it stops (Figs 3*B* and 8) is good evidence of a thrombosis. The complete lack of filling of a vessel does not necessarily mean that the thrombosis is complete (Fig. 8). The phlebogram can be of value in demonstrating a return circulation from an area apparently deprived of its arterial blood supply (Case 8). On the other hand, the mere filling of a vessel does not exclude the presence of thrombosis (Fig. 8); one also must consider irregularities in the diameter of the vessel (Fig. 12*B*).

When, as in Case 1, the middle cerebral artery, which is normally seen, failed to show in spite of filling of the anterior and posterior cerebral arteries and in the presence of an obvious thrombus of the opposite internal carotid artery, it seems safe to say that the middle cerebral artery was also involved in the disease process, even in the absence of focal signs at the time.

A rare condition already mentioned is met with in congenital absence of one or of both internal carotid arteries. It would be pure coincidence if such a condition were associated with a hemiplegic syndrome; of course, the characteristic stump of the thrombosed internal carotid artery would not be seen.

Although cerebral angiography enables one to see such fine details as local encroachment into the lumen of the vessel, it is not of much help as far as small cortical vessels are concerned. They are too inconstant in their topography, in the

21. See case listed in "Addendum."

22. See also cases listed in "Addendum."

way they branch, and too irregular in the way they fill with dye to enable one to tell in a given case whether the lack of filling is merely accidental or whether some are thrombosed. Furthermore, a "normal-appearing arteriogram" is not sufficient evidence for the statement that there is no thrombosis among the smaller vessels.

3. Diagnosis

There are no symptoms or signs which can be said to be pathognomonic of an occlusion of the internal carotid artery. Alone, the arteriogram, combined with an air study of the ventricular system, enables one to make a diagnosis of thrombosis of the internal carotid artery. However, in a case of hemiplegia, a decrease or loss of pulsation of the carotid artery on the involved side strongly favors the diagnosis of thrombosis.

Differential Diagnosis.—Disseminated sclerosis may be taken into consideration in cases with a history of recurrent episodes.[10] However, for the most part, the strictly unilateral symptoms that are found would be atypical of disseminated sclerosis. The observed nystagmoid jerks have not the regularity of true nystagmus. Transient paresis of the lateral eye movements is rare; indeed, we have not seen any; nor have the typical tremor and the speech difficulty been reported. The cerebrospinal fluid findings, also, are different in the two conditions.

In cases of progressive onset of hemiplegia preceded by headache, dizziness, and impairment of memory, the diagnosis will generally be one of intracranial expanding lesion (neoplasm, subdural hematoma). Although we have not observed it, papilledema, as well as vomiting, has been reported in cases of thrombosis. To differentiate the two conditions may at times be very difficult, as shown by Case 19 of Krayenbühl and Weber[6]: A man aged 48 had been suffering for 18 months from spells of weakness of the left side, which resulted in spastic hemiparesis. There was slight choking of the optic disks. The arteriogram showed an obstruction of the right internal carotid artery at the base of the skull. Thrombosis was suspected, but the ventriculogram disclosed an expanding lesion, which proved to be a parasagittal meningioma, weighing 125 gm. This case demonstrates well the necessity of pneumography.

Patients suffering from hemiplegia, with or without aphasia, seem to exhibit relatively less mental alteration in the presence of a thrombotic lesion than patients with expanding lesions, such as neoplasm, subdural, or intracerebral hemorrhage. This applies also to the patients in whom an apoplectic onset has been the characteristic feature. The main problem in differential diagnosis is not so much between thrombosis and neoplasm as between thrombosis and intracerebral hemorrhage.

II. Thrombosis of the Middle Cerebral Artery

1. Report of Cases

The considerations which lead one to perform an arteriographic study in cases of suspected blockage of the carotid artery are actually all that are needed to elucidate the patient's condition clinically. It may be of some interest, however, to compare the symptoms and signs presented in cases of involvement of the middle cerebral artery alone with those accompanying obstruction of the internal carotid artery. To this end, four case histories of patients who had occlusion of branches of the middle cerebral artery are reported.

CASE 7.—J. W., aged 47, was admitted to the medical ward on Sept. 24, 1936, with a history of hypertension. He had collapsed at work on the morning of admission, after which he was unable to speak and became rather stuporous. Physical examination at this time showed the right pupil to be larger than the left; there were right hemiplegia, right hemianesthesia, and right homonymous hemianopia. The blood pressure was 160 systolic and 100 diastolic. The Wassermann reactions of the cerebrospinal fluid and blood were negative; the blood count and blood chemistry were normal. Roentgenograms of the chest and skull revealed no abnormality. Lumbar puncture showed an initial pressure of 145 mm. of water on the day of admission. The fluid was said to have been grossly bloody. The patient made a gradual recovery while on the medical service. The blood pressure improved after one week, and the spinal fluid was clear and straw-colored on Oct. 14. He was transferred to the neurological division on Oct. 22, when he was able to speak fairly clearly and showed no

Fig. 11 (Case 7).—Incomplete filling of branches of middle cerebral artery.

evidence of hemianopsia. The fundi presented early arteriosclerotic changes. He was able to move his right leg slightly, but his right arm remained paralyzed. Impaired sensibility was reported for pain (pinprick) and touch and for two-point discrimination over the right side of the body; position and vibration sense were normal.

Arteriography, performed on Oct. 30, showed no abnormality on the right side. On the left side, the arterial system was well visualized except for the inferior division of the Sylvian group (Fig. 11), according to the roentgenologist, Dr. A. E. Childe. "This (the arterial system) is seen for only about 4 cm.; beyond that point it seems to be obliterated. The appearance is compatible with the obliteration of the inferior division of the Sylvian group on the left side." Whether or not one considers this case one of hemorrhage or of thrombosis, the focal nature of the signs is impressive.

CASE 8.—F. D., aged 31, for three weeks had experienced severe frontal and occipital headaches. The night before admission his wife had left him for a few hours and returned

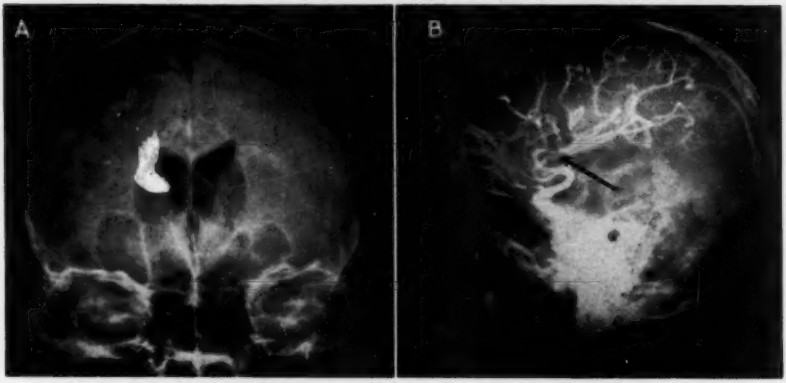

Fig. 12 (Case 8).—*A*, slight dilatation of left anterior horn. *B*, localized encroachment on lumen of branch of middle cerebral artery (arrow). The anterior cerebral group is not demonstrated. Note large ophthalmic artery and early branching of the middle cerebral artery.

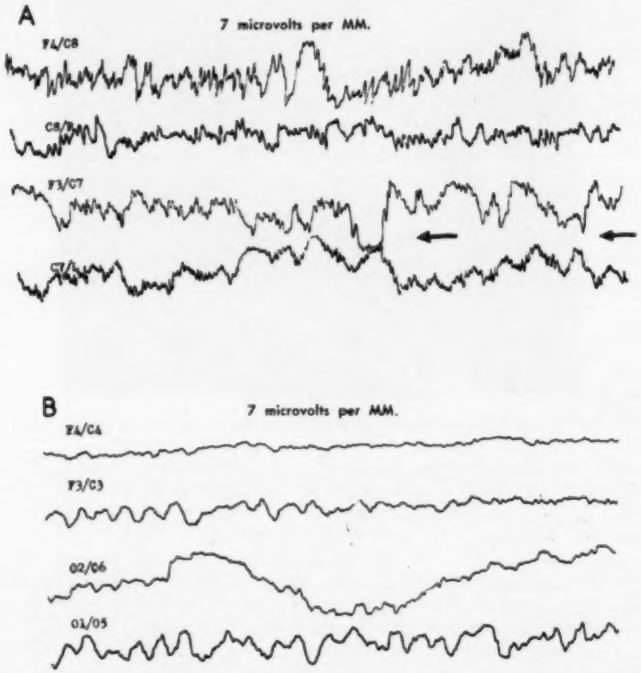

Fig. 13 (Case 8).—Random slow waves (*A*, third and fourth lines; *B*, second and fourth lines) and rhythmic discharges at frequencies between 2 and 6 per second recorded over large area of left hemisphere, with maximal phase reversals in left temporal region (arrows).

to find him sitting in a chair, somewhat dazed and unable to speak. Soon he was able to understand all she said but could not utter a word. Examination on his admission revealed bilateral venous engorgement of the ocular fundi, weakness of the right side of the face, complete motor aphasia, and slight paralysis of the right arm and hand and of the right leg. Hyperreflexia was present on the right with plantar extension. The cerebrospinal fluid pressure was normal; proteins were 41 mg. per 100 cc., and the Pandy reaction was negative. There were an increased sedimentation rate and a reduction in polymorphonuclear leucocytes, with a slight shift to the left. X-ray pictures of the skull, sinuses, and chest showed nothing noteworthy. For two weeks the patient had a spiking elevation of temperature, which then entirely disappeared.

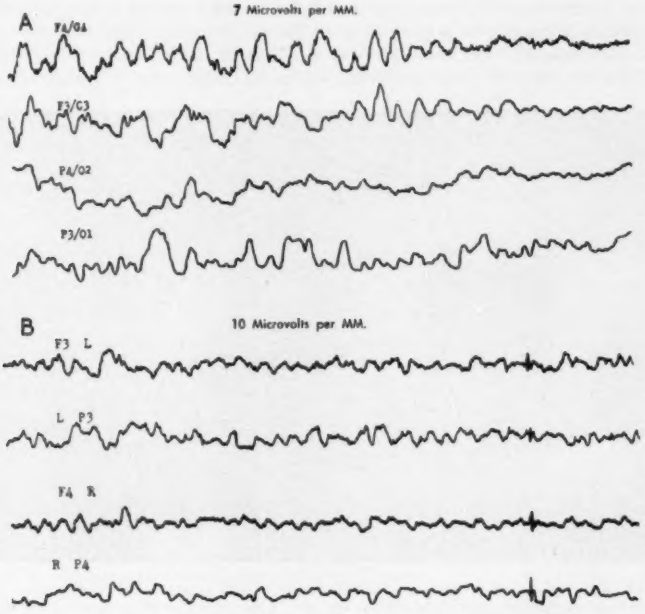

Fig. 14 (Case 8).—*A*, bilateral rhythmic disturbances of increased amplitude as compared with those shown in Figure 13*B*. *B*, burst of random slow waves from both hemispheres of lower voltage than those shown in Figure 14*A*.

A ventriculogram showed no evidence of an expanding intracranial lesion. The posterior portion of the left lateral ventricle was larger than the corresponding portion of the right. The left anterior horn was fractionally larger than the right one (Fig. 12*A*).

Arteriogram (iodopyracet [diodrast®], Aug. 19, 1947): The internal carotid artery was normal in appearance. The ophthalmic artery, and the anterior choroidal artery were well demonstrated. The middle cerebral artery was seen to break up into its main branches. One branch, probably the left frontoparietal branch of the middle cerebral artery, appeared to have a filling defect (Fig. 12*B*) just beyond the point at which the ascending frontal branch is given off. However, dye did pass, and the terminal branches seemed clear. This filling defect may have represented thrombosis. Although the anterior cerebral artery was not demonstrated with certainty, dye may have passed through it, for the inferior longitudinal sinus was well filled on the second film.

The electroencephalogram (Aug. 19, 1947) (Fig. 13) recorded random slow waves and rhythmic discharges at frequencies between 2 and 6 cps over a rather large area of the left hemisphere, but with maximal phase reversals in the left temporal region. A week later, on Aug. 26, a second electroencephalogram (Fig. 14*A*) showed evidence of deterioration since the previous examination. An examination on Sept. 3 (Fig. 14*B*) revealed definite improvement. Neurological examination at the time of discharge showed almost complete regression of symptoms and signs.

CASE 9.—G. C., aged 48, had been hospitalized on many occasions for certain genitourinary complaints. She was admitted in the summer of 1946 for a pyloroplasty. The patient was known to be alcoholic. In December, 1946, she was readmitted, with complaints of increasing nervousness and tremor of both hands. Examination showed absence of the deep reflexes and hypoactive superficial reflexes. In other respects it revealed nothing abnormal in particular, no disturbance of the cardiovascular system. The blood pressure was 142 systolic and 60 diastolic. No diagnosis was made, and she was kept in the hospital for observation. On Jan. 4, 1947, the patient, who had been feeling well on the previous day, was found lying motion-

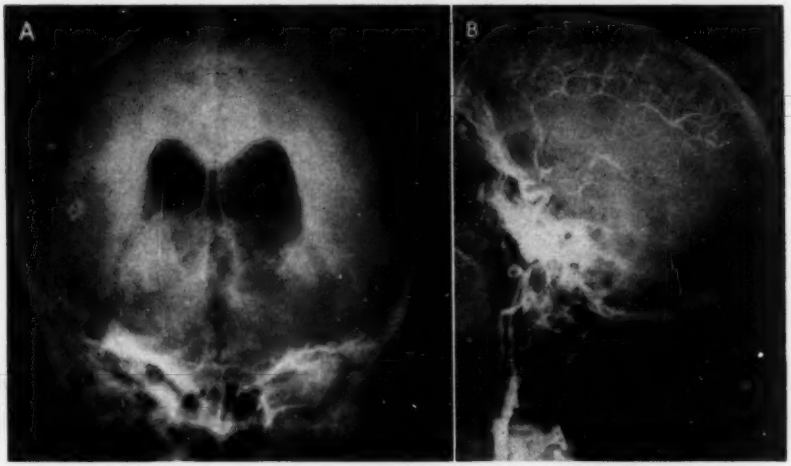

Fig. 15 (Case 9).—*A*, especially marked dilatation of left anterior horn; abnormal subarachnoid collections of oxygen over both frontal regions (note cavum septi pellucidi). *B*, narrowing of left internal carotid artery, commencing 1.5 cm. distal to bifurcation of common carotid artery. The artery again tapers from the anterior clinoid process toward the Sylvian fissure. The dye has failed to pass beyond a short segment 1 cm. in length into the middle cerebral artery and some deep branches.

less in bed. Examination revealed motor aphasia; all that the patient could say was "yes" and "no," and complete hemiplegia was present on the right side, involving, to a less extent, the lower part of the face. The tongue protruded to the right.

The electroencephalogram (Jan. 10) showed slow waves from the left hemisphere over a fairly wide area, as well as from the left-ear electrode, suggesting an origin deep to the central and temporal region. No significant slow-wave disturbances were recorded from the right hemisphere. There was asymmetry in the alpha activity, there being an apparent depression of alpha waves from the right central and parietal region.

The pneumoencephalogram (Jan. 24) showed moderate dilatation of the ventricular system with marked dilatation of the anterior horn on the left (Fig. 15*A*).

The arteriogram taken with thorotrast® (Feb. 19) demonstrated narrowing of the left internal carotid artery beginning at a point 1.5 cm. distal to the bifurcation of the common

carotid artery. The artery again tapered from the anterior clinoid process back toward the Sylvian fissure, and no dye could be seen in the middle cerebral artery beyond a short segment, measuring about 1 cm. in length. The anterior cerebral vessels were fine and tortuous and showed rather complete filling (Fig. 15*B*).

After a period of definite improvement in speech and motor function, especially in the leg, the patient's condition became worse. Fifteen months later, she had a generalized epileptic seizure. Hemiplegia became complete, and there was a marked deterioration of her mental condition.

CASE 10.—M. N., a boy aged 6 years, was admitted on July 17, 1948. Three weeks before he had complained to his mother that he could not walk. She noticed that his right leg was partially flexed and spastic. He complained of pain in the limb. After 15 minutes the spell passed off, and he carried on normally. He had two similar attacks, which were not associated with headache. On the day of onset of his present trouble he played normally all day. In the evening he complained of sudden headache. His mother noticed that his head was "hanging loosely," that his mouth was drooping, which apparently prevented him from talking, and that

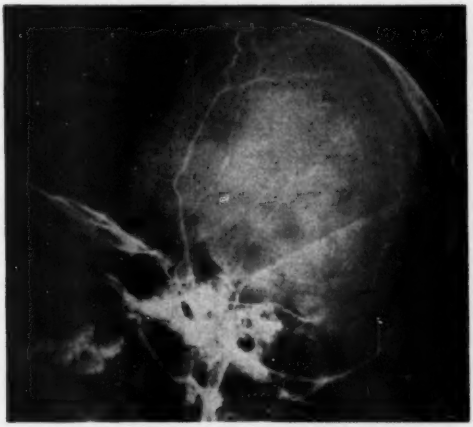

Fig. 16 (Case 10).—Narrowing of intracranial portion of internal carotid artery. Only a segment of one branch of the middle cerebral artery is seen.

he had become weak on his right side. He did not lose consciousness and remembered what had happened. One hour later he vomited.

On examination the child appeared to be intelligent but had motor aphasia, questionable right homonymous hemianopsia, and right hemiparesis, which included the face, arm and leg and was more pronounced in the upper limb. Tendon reflexes were depressed, but the plantar response on the right side was of extensor type.

The urine was normal. The Wassermann reactions of the blood and the cerebrospinal fluid were negative. The cerebrospinal fluid was clear, and colorless, and there were no cells. The protein content was 27 mg./per 100 cc. Cerebrospinal fluid pressure was 150 mm. Hg. Blood tests showed a slightly increased sedimentation rate and leucocytosis, with increase in neutrophils and eosinophils.

A pneumoencephalogram (July 23, 1948) showed dilatation of the lateral, third, and fourth ventricles and basal cisterns, with practically no filling of the subarachnoid spaces. There was a slight shift of the septum pellucidum from left to right, associated with some smallness of portions 2 and 3 of the left lateral ventricle.

In an electroencephalogram (July 21), the normal background activity in the left hemisphere was masked by high voltage, ½ to 3 per second delta waves. These showed the highest voltage

in the left parieto-occipital region, with phase reversals in the central and posterior parietal regions. Slow waves were transmitted to the right hemisphere, where they were superimposed on normal background alpha activity.

In an arteriogram taken with iodopyracet (Aug. 9), the left common carotid artery appeared normal and pulsated. Stereoscopic films showed narrowing of the left internal carotid artery in its intracranial portion up to the origin of the ophthalmic artery. Visualization of the middle cerebral tree was greatly impaired. In fact, only a segment of one branch of the middle cerebral artery was seen. The anterior cerebral group was not visualized (Fig. 16). It is well known, of course, that this arterly frequently does not fill. Disease at least of the internal carotid, the middle, and possibly the anterior cerebral arteries, associated with thrombosis, was suspected.

2. Clinical Analysis

All four cases fall into the group of hemiplegia of sudden onset. However, such a small number of cases does not warrant any conclusion as to whether thrombosis of the branches of the internal carotid artery has only that mode of onset and evolution. Furthermore, in the last two cases, there was most probably also partial thrombosis of the internal carotid artery, since narrowing of this vessel was shown by arteriography. The clinical picture did not differ essentially from the symptomatology in the cases of thrombosis of the internal carotid artery which we have discussed. There was predominantly a motor hemiplegic syndrome, which might be associated with hemianesthesia (Case 7) and with a homonymous hemianopsia (Cases 7 and 8, and perhaps Case 9). Pneumographic studies performed in the last three cases showed moderate to marked partial dilatation of the homolateral ventricle in Cases 8 and 9 and dilatation of the whole ventricular system in Case 10, with some decrease in size of the anterior part of the left lateral ventricle, associated with a slight shift of the septum pellucidum toward the right, interpreted as due to edema. That similarity was again found in the electroencephalogram. Slow waves of various amplitudes masked the normal background over the involved area. As shown in Case 8, the electroencephalographic findings corresponded well with the clinical picture, and the return to normal electrical activity corresponded closely to the clinical improvement. Reviewing these facts, it must be said that there is not a single neurological, roentgenographic, ventriculographic, or electroencephalographic sign which could be said to be pathognomonic of thrombosis of one or the other branch of the internal carotid artery which could not occur when the thrombus is located in the internal carotid artery itself, and vice versa. The only means of locating the thrombosis, aside from careful palpation of the carotid pulsation, is cerebral angiography. In the present stage of our ability to interpret arteriograms, cerebral angiography will fail to reveal thrombosis of small cortical vessels. That the hemiplegic syndrome we are now familiar with might occur in cases of such lesions is shown by Davis and Perrit's report [23] on 11 cases of thromboangiitis obliterans involving cortical vessels, in which hemiplegic symptoms of a space-occupying lesion were present. In nine of their cases the diagnosis was made by direct visualization at operation. Arteriograms apparently were not performed, but in one instance, in which autopsy followed, thrombosis of the internal carotid artery was found.

23. Davis, L., and Perrit, G.: Cerebral Thromboangiitis Obliterans, Brit. J. Surg. **34**:307-313 (Jan.) 1947.

The differential diagnosis of thrombosis of the internal carotid artery and congenital absence of this vessel should not present a problem. As stated above, the occurrence of a hemiplegic syndrome in the latter is purely coincidental, obviously not being due to the absence of the carotid artery.

III. ETIOLOGICAL FACTORS LEADING TO THROMBOSIS OF THE INTERNAL CAROTID ARTERY

Occlusion of the internal carotid artery may have several causes.

1. An embolus from the heart or the proximal part of the aorta, or from a so-called paradoxical embolus.

2. Thrombosis. This is a more frequent cause and may result from a variety of lesions.

(*a*) Thrombosis can develop in retrograde fashion from ligation of the external carotid or the thyroid artery, and it may follow ligation of the internal carotid artery itself or may proceed from a thrombosed aneurysm of the aorta or of the common carotid artery.

(*b*) Thrombosis is often due to arteriosclerosis and involves especially the most proximal and distal portions of the internal carotid artery. It occurs generally in older people who present evidence of arteriosclerosis elsewhere in the vascular system (Case 6).

(*c*) Buerger's disease (thromboangiitis obliterans) is found chiefly in younger persons. Histologically verified cases have been reported in detail by Krayenbühl and Weber,[6] Krayenbühl,[7] Andrell,[5] Scheinker,[24] and Lindenberg and Spatz.[25] Frøvig [26] reported in detail a case of bilateral obliteration of the common carotid artery, probably on the basis of thromboangiitis obliterans. Actually, of 17 cases in which a specimen of the thrombosed internal carotid artery was examined histologically, Krayenbühl and Weber [6] found 10, all of men, in which the typical lesion of thromboangiitis obliterans was present. Five patients were between 40 and 50, and five between 50 and 60 years of age. The authors stated that the thrombosis of the internal carotid artery seen in thromboangiitis obliterans is but part of a more generalized cerebral thromboangiitis. Davis and Perrit [23] suggested that the thromboangiitis obliterans involved for the most part the smaller arteries of the convexity, thrombosis of the internal carotid artery being the result of secondary thrombosis, similar to the obstruction found in the brachial and femoral arteries. Of their 11 cases, a craniotomy was performed in 9: "The distal portion of many of the smallest pial arteries in the exposed area of the brain were white and obliterated for a distance of 1 or 2 cm. They were worm-like white strings."

(*d*) Acute infections may also play a part. King and Langworthy [9] described the case of a 7-year-old boy in whom thrombosis of the right internal carotid artery developed three weeks after pneumonia.

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24. Scheinker, I. M.: Cerebral Thromboangiitis Obliterans, Histogenesis of Early Lesions, Arch. Neurol. & Psychiat. **52**:27-37 (July) 1944.

25. Lindenberg, R., and Spatz, H.: Über die Thromboendarteriitis obliterans der Hirngefässe (cerebrale Form der v. Winiwarter-Buergerschen Krankheit), Virchows Arch. path. Anat. **305**:531-557, 1939.

26. Frøvig, A.: Bilateral Obliteration of the Common Carotid Artery: Thromboangiitis Obliterans, Acta psychiat. et neurol., Supp. 39, 1946.

(*e*) Thrombosis may have a syphilitic origin. Moniz [2] described such cases. Krayenbühl and Weber [27] had one case of thrombosis of the internal carotid artery in a syphilitic patient. However, histological examination of the vessel showed merely nonsyphilitic angiitis.

(*f*) Thrombosis may be due to direct trauma, as described by Löhr.[28]

(*g*) Thrombosis may be due to a pathological condition of neighboring tissue, as reported by Krayenbühl and Weber.[6]

3. External compression of a neoplasm.

IV. PATHOGENESIS OF THE CLINICAL SYNDROME

It is a common opinion, which has recently been expressed again by Govons and Grant,[10] that thrombosis of the internal carotid artery may be a "source of neurological disturbance." However, neurosurgical experience of the past 10 or 12 years with ligature of the carotid artery in cases of intracranial aneurysm has shown that occlusion of the internal carotid artery is not fraught with danger to life and generally does not give rise to neurological disturbances. Cases have also been described by Govons and Grant [10] in which thrombosis of the internal carotid artery was an unexpected finding, not being associated with abnormal neurological signs. It is therefore justifiable to conclude that thrombosis of the internal carotid artery per se does not necessarily produce a hemiplegic syndrome.

Detailed clinicopathological studies of vascular lesions by various observers (Foix and associates,[29] Critchley,[30] Davison and associates [31]) have shown the relationship of all the neurological signs we have described in our cases to the involvement of particular branches of cerebral vessels. In other words, the hemiplegic syndrome met with in patients with thrombosis of the internal carotid artery borrows its elements from the syndromes of cerebral vessels. This only confirms our previous statement, and we can say now that there is not necessarily any direct causal relationship between thrombosis of the internal carotid artery and the hemiplegic syndrome.

The question of an indirect causal relationship consists in asking whether a thrombus within the internal carotid artery can actually produce secondary changes in the cerebral vessels and the brain substance. Several possibilities have been proposed: (*a*) embolization from the thrombus (Herfarth [32]); (*b*) extension of the

27. Krayenbühl, H., and Weber, G.: Personal communication to the authors, 1948.

28. Löhr, W.: Hirngefässverletzungen in arteriographischer Darstellung: II. Thrombotische Verstopfungen und Zerreissungen von Gefässen des Gehirns, Zentralbl. f. Chir. **63**:2593-2608 (Oct. 31) 1936.

29. (*a*) Foix, C., and Levy, M.: Les ramollissements sylviens. Syndromes des lésions en foyer du territoire de l'artère sylvienne et de ses branches, Rev. neurol. **2**:1-51 (July) 1927. (*b*) Foix, C., and Hillemand, P.: Les syndromes de l'artère cérébrale antérieure, Encéphale **20**:209-232 (April) 1925. (*c*) Foix, C., and Masson, A.: Le syndrome de l'artère cérébrale postérieure, Presse méd. **31**:361-365 (April 21) 1923.

30. Critchley, M.: The Anterior Cerebral Artery and Its Syndrome, Brain **53**:120-165 (July) 1930.

31. Davison, C.; Goodhart, S. P., and Needles, W.: Cerebral Localization in Cerebrovascular Disease, Arch. Neurol. & Psychiat. **30**:749-774 (Oct.) 1933.

32. Herfarth, H.: Zur präliminaren Unterbilding der Anteria carotis externa, Zentralbl. f. Chir. **53**:1106-1107 (May 1) 1926.

thrombosis distally into the branches of the internal carotid artery (Löhr [28]); (*c*) spasms of the cerebral vessels induced by impulses originating in the diseased carotid artery (Andrell,[5] Leriche [33]) or via the cervical ganglion (Sunder-Plassman [34]), and (*d*) a slowing down of the blood flow in the peripheral branches, producing stasis and ischemia (Kinnier Wilson [35]). However, in the light of the results of ligation of the internal carotid artery and of observations in asymptomatic cases of thrombosis of the carotid artery, spasm and stasis are not likely to play an important role. An indirect causal relationship is thus possible but is certainly by no means the rule. As a matter of fact, in the majority of cases in which thrombosis of the internal carotid artery is part of a generalized vascular disease, it is more likely that the thrombosis of the internal carotid artery is not related at all to the hemiplegic syndrome, the latter being due to the independent involvement of cerebral vessels. Davis and Perrit [22] even went so far as to state that involvement of the internal carotid artery in cerebral thromboangiitis obliterans is secondary to the thrombosis of small cortical vessels.

The foregoing considerations make it obvious that such terms as "carotid hemiplegia" and "syndrome of thrombosis of the internal carotid artery" are inaccurate. Their use may be justifiable from a practical clinical viewpoint, since the diagnosis in early cases rests generally upon the arteriographic demonstration of the thrombosis within the internal carotid artery. The term "syndrome of the internal carotid system," however, seems to us more accurate.

V. THERAPY AND PROGNOSIS

There is, of course, no good treatment for thrombosis of the internal carotid artery, but attempts have been, and are still being, made to influence the blood supply from the other side of the brain and to eliminate reflex spasms in the still patent cerebral branches. M. and D. Schneider,[36] using the thermostromuhr of Rein on dogs, found that the ligation of one common carotid artery or of the external carotid artery (proximal to the bifurcation of the middle meningeal artery) would increase the blood flow in the opposite common carotid artery from 80 to 100% of its previous value. This would not occur after ligation of the internal carotid artery alone or of the external carotid artery distal to the middle meningeal artery (so-called meningeal reflex). On the basis of Schneider's experiments and Leriche's [33] theory that "an obliterated artery ceases to be an artery and becomes a diseased sympathetic nerve," Krayenbühl and Weber [6] removed in some cases a portion of the thrombosed artery, denervated the carotid sinus, and ligated both the external and the common carotid artery. The follow-up observation in their cases, however, was too short to warrant any conclusion as to the effectiveness and the advisability of such measures. These authors stated the belief that this procedure, if it is to have

33. Leriche, R.: Experimental and Clinical Basis for Arterectomy in Treatment of Localized Arterial Obliterations, Am. J. Surg. **14**:55-67 (Oct.) 1931.

34. Sunder-Plassman, P.: Endangitis obliterans des Gehirns, Deutsche Ztschr. f. Chir. **254**:463-487, 1941.

35. Wilson, S. A. K.: Neurology, edited by A. Ninian Bruce, Vols. I and II, London, Edward Arnold & Company, 1940, pp. 1838.

36. Schneider, M., and Schneider, D.: Untersuchungen über die Regulierung der Gehirndurchblutung, Arch. exper. Path. u. Pharmakol. **175**:606-639, 1934; II. Einwirkung verschiedener Pharmaca auf die Gehirndurchblutung, ibid. **175**:640-664, 1934; III. Die Rolle des Carotissinus bei der Regulierung der Gehirndurchblutung, ibid. **176**:393-400, 1934.

success, must be carried out in the early stages of the disease. Chao and associates [17] also recommended excision of the thrombosed artery and denervation of the carotid sinus if the latter proved to be hypersensitive. More direct action upon the sympathetic nervous system was advised by Sunder-Plassman,[34] who removed the chain bilaterally. The prognosis depends mainly upon the basic illness. Even in cases in which the hemiplegic syndrome is not severe or absent, the fact that a thrombosis has occurred in the internal carotid artery makes it probable that sooner or later further thrombosis of cerebral vessels will occur, with the ensuing neurological disturbances.

VI. CONCLUSIONS

A few facts emerge from the foregoing considerations and may be summarized as follows:

Neurological Syndrome.—The neurological syndrome is characterized by hemiparesis on the side opposite the lesion, involving chiefly the upper limb, then the face, and, to a less degree, the leg. There may be sensory disturbances, which consist in impairment of cortical sensation and in severer cases may involve all types of sensation. Impairment of vision is frequent and may be due either to vascular disturbances within the eyeball or to involvement of the optic radiation. With the former the visual acuity will be impaired; with the latter, the visual field.

It is our experience that the mental state of the patients is relatively well preserved. Aphasia results if the lesion is on the dominant side.

Roentgenologic Findings.—No pathological features are disclosed, as a rule, in plain roentgenograms of the skull. The position of the pineal gland should be determined. Films of the chest, abdomen, and limbs should be taken when general vascular disease is suspected.

Pneumoencephalography.—Air studies may disclose enlargement, and generally asymmetry, of the ventricles, the ipsilateral ventricle being most enlarged. The pineal gland may not appear displaced. However, a slight shift may occur toward the side of an old atrophic lesion, as in Case 1, or toward the opposite side at a stage when ipsilateral cerebral edema is still present, as shown in Cases 3, 5, and 10, approximately 3, 12, and 6 days, respectively, after immediate onset of signs.

Electroencephalography.—Abnormal slow waves, such as are characteristic of degenerative or destructive lesions, are recorded from the ipsilateral hemisphere, usually from the frontotemporal region. Attention must be paid to the occipital alpha activity and the electrical activity of the opposite hemisphere.

Arteriography.—This method enables one to localize the inferior limit of the thrombosis. It must be remembered that failure of the artery to fill with dye does not necessarily mean that there is a thrombus. The characteristic appearance of a thrombotic occlusion in the arteriogram is a cone-shaped narrowing of the vessel. The block in the carotid artery is most commonly found near the bifurcation of the common carotid artery, the next commonest place being in or near the petrous portion of the temporal bone.

Diagnosis.—This consists mainly in distinguishing between a space-occupying lesion (neoplasm, abscess, subdural or epidural hematoma, or intracerebral hemorrhage) and an occlusive vascular process. The mode of onset and the evolution, as

well as the patient's mental state in relation to the hemiplegic syndrome, often allow one to diagnose a thrombosis clinically. The only physical sign which enables one to locate it in the internal carotid artery, rather than in one of its branches, is a decrease or a loss of the carotid pulsation. Final evidence of a thrombosis, aside from operative procedures, will be given by cerebral arteriography combined with pneumoencephalography.

Etiology.—The etiological factors are multiple. From the study of the literature, however, it seems that the two most frequent known causes are arteriosclerosis and thromboangiitis obliterans.

Pathogenesis.—There is no direct causal relationship between a thrombosis of the internal carotid artery and the neurological picture. Symptoms and signs depend upon which of the cerebral branches is or are involved. This involvement may be secondary to a thrombosis of the internal carotid artery, but oftener, in our opinion, both are independent manifestations of the same disease.

Therapy.—Treatment aims to increase the collateral blood flow from the opposite side and to prevent vasoconstriction on the same side. Krayenbühl's method, which combines periarterial sympathectomy, including denervation of the carotid sinus (sometimes with removal of a portion of the thrombosed internal carotid artery), and ligature of the common and external carotid arteries, needs further clinical trial. The place of anticoagulant therapy is not yet established.

Terminology.—The terms "carotid hemiplegia" and "syndrome of thrombosis of the internal carotid artery" are inaccurate, since the clinical syndrome is not directly due to the involvement of this artery. Their use may, however, be justified for practical purposes in the cases in which they correspond to and describe the arteriographic finding on which the diagnosis rests. Syndrome of occlusion within the internal carotid system seems to us a better term.

VII. SUMMARY

Six cases of thrombosis of the internal carotid artery and four cases of thrombosis of its branches are reported. The clinical syndrome and its significance are discussed with reference to the literature.

VIII. ADDENDUM

Since this article was written, occlusion of the internal carotid artery has been demonstrated by arteriography in three more cases. The first patient, a man aged 43, had onset of left hemiplegia and mental confusion three days after hemorrhoidectomy, performed under spinal anesthesia produced with tetracaine. Twitching movements of the left hand occurred, and the eyes turned to the right. Confusion improved after three weeks. Three months after the onset a series of convulsive seizures occurred.

An arteriogram (iodopyracet, 35%; open exposure) taken four months after the incident demonstrated occlusion of the internal carotid artery at its origin. An electroencephalogram indicated a destructive lesion in the right hemisphere and depression of alpha rhythm. An encephalogram showed some dilatation of the right lateral and third ventricles, indicating atrophy of the right cerebral hemisphere with some shift to the midline structures to the right.

The second patient, a man aged 28, had had a sudden onset of right hemiplegia with aphasia nine years before admission. Improvement occurred over two years. Several months before his admission gradually increasing paralysis of the fingers of the right hand took place, followed, some months later, by recurrent weakness of the right leg. He experienced a subjective disturbance in the left index finger, with increase of stiffness of the left hand, similar to that which he had suffered on the right side. General deterioration supervened, with increasing paralysis and death.

An electroencephalogram showed evidence of generalized cerebral dysfunction. An encephalogram showed generalized atrophy of the left hemisphere with enlargement of the left lateral ventricle and deepened subarachnoid markings, at least over the left parietal region.

Arteriography (injection of iodopyracet, 35%, open exposure) showed good pulsation in each common carotid artery but revealed blockage of the internal carotid artery at the level of the carotid canal on the left, with thinning of the artery in the neck. There were demonstrated also irregularities in the walls of the intracranial portion of the right internal carotid artery, suggesting periarteritis nodosa (essential polyangiitis), though there was filling of the anterior and the middle cerebral arteries.

A third patient, with pronounced partial blockage of the middle cerebral supply (as shown by arteriography) with electrographic evidence and characteristic symptoms and signs of left motor and sensory hemiplegia and left homonymous hemianopsia, was shown to be suffering from polycythemia vera.

ELECTRIC SHOCK THERAPY IN A CASE OF MYASTHENIA GRAVIS COMPLICATED BY A SCHIZOPHRENIC PSYCHOSIS

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MYASTHENIA gravis is a rather uncommon entity. There were 25 admissions with myasthenia gravis in a total of 28,000 general admissions to the Columbia-Presbyterian Medical Center in 1948. Eaton,[1] in 1947, reported an incidence of four cases of myasthenia gravis per 10,000 admissions to the Mayo Clinic.

The combination of myasthenia gravis and psychosis is a rare occurrence. Very few cases have been reported in which a psychosis has been associated with myasthenia gravis. Göni,[2] in his exhaustive study of the literature, did not report any cases of myasthenia complicated by psychotic episodes. In 1939 Collins[3] described a case of schizophrenia in a patient with myasthenia gravis. In 1945 Delgado and Sal y Rosas[4] reported a case of myasthenia gravis with psychosis. The authors did not classify the psychosis, but simply mentioned symptoms of paranoid ideas, visual and auditory hallucinations, and periods of disorientation and confusion. Eaton[1] found six cases of psychiatric disorders among 175 myasthenic patients—one of a manic-depressive psychosis, two of a "schizoid reaction," and the other three of psychoneuroses.

Our interest in this subject was stimulated by our recent observation of a woman aged 20 who had had myasthenia gravis for eight years and who during the last year manifested a schizophrenic psychosis. The symptoms of myasthenia began at the age of 10 or 11 years. Göni[2] states that the onset of myasthenia gravis in childhood is not unusual.

It became apparent that the patient was in need of shock therapy for the schizophrenic disorder. The question arose whether the myasthenia gravis constituted a contraindication to the electric shock treatments. In a brief survey of the literature, we encountered only the report of Eaton,[1] who had applied electric

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1. Eaton, L. M.: A Warning Concerning Use of Curare in Convulsive Shock Treatment of Patients with Psychiatric Disorders Who May Have Myasthenia Gravis, Proc. Staff Meet., Mayo Clin. **22**:4-7 (Jan. 8) 1947.

2. Göni, A. R.: Myasthenia Gravis, Baltimore, Williams & Wilkins Company, 1946.

3. Collins, R. T.: Psychiatric Syndromes in Myasthenia Gravis, Brit. M. J. **56**:975-977 (May 13) 1939.

4. Delgado, H., and Sal y Rosas, F.: Un caso di miastenia con psicosis, Rev. neuro-psiquiat. **8**:26-33 (March) 1945.

shock treatments in three cases of psychiatric disorders complicated by myasthenia gravis. In one of the cases seven electric shock treatments were given, four of which resulted in grand mal seizures. We felt that the psychiatric indications for therapy in our patient were so strong that they outweighed the possible contraindications and risks imposed by the myasthenia. We believed that a report of this case would be worth while because of our experience in the treatment of the schizophrenic psychosis.

PRESENTATION OF CASE

History.—A white woman aged 20 had been treated for myasthenia gravis for eight years. She was admitted for the first time to the Neurological Institute of New York on April 4, 1950. The present illness became acute shortly before her admission to that hospital. The patient was traveling with her parents in Europe when she became severely disturbed. She became suspicious and fearful and complained of hearing accusatory voices when she was in crowds. She felt that her parents were against her and that her father wanted to poison her. At times she became excited, overactive, and abusive in her accusations. At other times she was withdrawn and seclusive. This bizarre behavior necessitated her return to New York.

A detailed personality profile will not be given because it does not fall within the scope of this paper. Suffice it to say that for at least a year prior to the acute episode the patient had shown a gradual disintegration of personality. She had experienced increasing difficulty in concentrating, and, although she had been an excellent student, she suddenly failed in several subjects in college and eventually withdrew. She became increasingly withdrawn, seclusive, and preoccupied. Her interest in family and friends declined. She showed strong emotional lability but was predominantly depressed and suicidal. Her sleep was greatly disturbed.

The myasthenia gravis, which began about eight years prior to the present hospitalization, was manifested by generalized weakness, particularly by ptosis of the eyelids and easy fatigability in chewing and swallowing. The diagnosis was confirmed when the patient showed a striking improvement in response to appropriate doses of neostigmine. Her condition was regulated on a daily dose of 15 mg. of neostigmine bromide orally three to five times a day. Her symptoms showed some variation during the day, but she was able to carry on the usual activities of girls of her age without evidence of undue fatigue. She gave no history of respiratory distress or other signs of ever having had a myasthenic "crisis."

Examination.—The vital signs were normal. The patient was well nourished and asthenic and appeared younger than her stated age. There was a moderately severe acne eruption over the face and shoulders. There was a moderately severe degree of scoliosis of the thoracic and lumbar portions of the spine. The remainder of the general physical examination showed nothing abnormal.

The gait and station were normal. There was no weakness in the muscles of the trunk or extremities. There was a high degree of myopia in both eyes, but the visual fields were normal. She complained of double vision on lateral gaze in the "red-glass test." The pupils were round, regular, and equal and reacted normally to light and in accommodation. There was a tendency to poor coordination in the extraocular movements, and the extraocular muscles showed evidence of fatigue on repetitive testing. There was mild ptosis of both eyelids; this was more pronounced on the right. The rest of the neurological status was normal.

The patient exhibited bizarre behavior. She sat quietly in her room and moved about very little. When the examiner questioned her, she avoided his gaze by staring at the floor. She was reluctant to respond to questions and answered in a stereotyped manner with a curt "yes" or "no." She appeared preoccupied and at times resentful of the examiner's intrusion. Suicidal ideas were admitted, and the patient appeared to be moderately depressed. At times her affect seemed incongruous. She described hallucinations but would not give any details except that she heard voices saying "mean things" to her. She admitted having had ideas of persecution and peculiar notions about her family but stated that she did not believe these ideas to be true at the time of the examination. There was no disturbance in orientation; no memory defects were noted. Her judgment was fair but fluctuated considerably. Insight was lacking most of the time.

Laboratory Data.—A complete blood cell count, urinalysis, and determination of the erythrocyte-sedimentation rate gave normal results. The basal metabolic rate and the electrocardiogram

were within normal limits. The blood calcium and phosphorus levels were normal. A roentgenogram of the chest showed no mediastinal mass or other abnormality. The electroencephalogram was interpreted as showing a mildly abnormal pattern, especially in response to hyperventilation. Roentgenograms of the spine revealed moderately severe scoliosis. The roentgenographic findings in the skull were within normal limits.

Psychological studies were made on the patient's admission and before her discharge. The psychologist reported that the intelligence quotient was 98 and was average for her intellectual functioning at that time. Suggestions of cerebral malfunction appeared in the various tests, but this was thought probably to be psychogenic. There was evidence of a profound personality disorganization, such as marked withdrawal, hostility, and hallucinations. Serious suicidal thinking was evident. The psychologist felt that the disturbance was severe but noted some response to stimulation and social contact.

Hospital Course.—The studies mentioned above were completed shortly after admission, and the diagnoses of myasthenia gravis and schizophrenia were made. It was felt that the patient would require electric shock treatments, but because of her myasthenia this procedure was not initiated without considerable deliberation. She was seen by several consultants, and it was

Upper illustration, patient before beginning the course of electric shock therapy. She had received her usual morning dose of neostigmine three hours before this photograph was taken. Ptosis is present in both eyes and is most pronounced in the right eye.

Lower illustration, patient immediately after electric shock treatment. She did not receive a "booster" dose of neostigmine before this treatment. Ptosis has almost completely disappeared.

finally decided that the indications for electric shock therapy presented by her schizophrenia outweighed any contraindications imposed by the myasthenia.

The patient was given 15 mg. of neostigmine bromide every three hours while awake. She received 75 mg. of adiphenine (trasentine®) with each dose to combat unpleasant smooth-muscle effects. She was given 20 electric shock treatments, spaced at intervals of two or three days, except for the last three treatments, which were given at weekly intervals. She received an intramuscular injection of 0.5 mg. neostigmine methylsulfate and 0.6 mg. of atropine about 15 min. before each treatment. An anesthetist was in attendance at each treatment and was prepared to intubate and give artificial respiration if such need arose. No other medicament was administered except for an occasional dose of secobarbital at bedtime. The treatments were uneventful; however, the duration of the seizures seemed longer than that usually seen. On two occasions her postseizure apnea was slightly prolonged, but it was felt that this was not unusual and was probably unrelated to her myasthenia. For the purpose of comparison, one treatment was given without the extra neostigmine and atropine. The patient was not restless or overactive immediately after the treatment, as she had been on previous occasions. A photograph was taken of her face

before the course of shock treatments, and another, immediately after she awakened from one of the treatments. In the first picture bilateral ptosis was very evident, but the second showed essentially no evidence of ptosis.

The patient gradually improved; she was less depressed and showed more interest in herself and her surroundings; she denied having hallucinations. Her personal appearance became more important to her. The patient conversed more easily, was less withdrawn, and was able to read and discuss political events with her nurse. She took short leaves from the hospital, attended by her nurse. On one occasion, however, she admitted that she still had suicidal thoughts. Repeated psychometric testing after the course of shock therapy showed observable shifts in function; for instance, the previously noted indications of cerebral malfunction were absent. The intelligence quotient was 99. Evidence of a severe personality disorder was still present. However, the tests showed changes for the better in her social and emotional orientation. The patient semed to have become more aware of her environment and was able to respond more appropriately to its stimulation. There were greater interest in people and a better realization of her role as a girl. Phantasies were still evident, but no hallucinations were noted. A week after her last treatment she was discharged to the care of the family. She has been seen on several occasions, and her improvement has been maintained.

COMMENT

The uneventful course of electric shock therapy in this case demonstrated that myasthenia gravis is not necessarily a contraindication to electric shock therapy. This is in agreement with the report of Eaton.[1] Nevertheless, we feel that certain precautions should be taken, as outlined above, to anticipate any complications when the concurrence of myasthenia and psychosis necessitates treatment with electric shock therapy.

In considering this problem, one might suppose that the vigorous muscular exertion during the convulsive seizure might readily cause the "myasthenic reaction." In this case such a reaction did not occur. Instead, the convulsion was longer than that seen in a patient who has no myasthenia and to whom neostigmine has not been given.

In each instance the ptosis disappeared after the convulsive seizure. This also occurred when the "booster" dose of neostigmine was omitted before the shock treatment. The over-all course of the myasthenia was not altered in this case, although there were short periods of improvement immediately after each treatment.

SUMMARY

A case is presented of a woman aged 20 with myasthenia gravis in whom schizophrenia developed. The rarity of this combination has been noted.

The patient was given 20 electric shock treatments, and no difficulties were encountered. Precautions taken in this case are outlined.

There was general improvement in the mental state of the patient. Short periods of improvement of the myasthenia followed immediately the electric shock treatments. No fundamental alterations in the myasthenia were observed.

ADDENDUM

Since the submission of this paper for publication, another psychotic episode of a similar nature developed.

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Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

CELL CONCENTRATION AND LAMINAR THICKNESS IN THE FRONTAL CORTEX OF PSYCHOTIC PATIENTS: STUDIES ON CORTEX REMOVED AT OPERATION. LEWIS P. ROWLAND and FRED A. METTLER, J. Comp. Neurol. **90**:255 (June) 1949.

Rowland and Mettler studied sections of cerebral cortex surgically ablated from 23 patients, of whom 22 were schizophrenic and one was manic-depressive. In the preparation of the tissues many precautions were used to insure the uniformity of the changes inherent in the methods. Cell counts were made only at the crowns of the gyri. Five counts were made from each layer of the cortex on each of five slides. The patients were of different age groups; some had severe mental disease and others less severe; some had been in an institution for more than 22 months and others less; some had received shock therapy, insulin, or metrazol,® and others had not. By comparing the cell counts for the selected areas of cortex of these contrasting groups of patients, the authors sought to answer the question whether there was significant histopathologic alteration in the cerebral cortex in schizophrenia. Rowland and Mettler conclude that their study shows no significant difference in cell counts in the various groups of patients and infer that postmortem swelling may have accounted for the appearance of the tissues, which some investigators have reported as being due to the dropping out of nerve cells.

ADDISON, Philadelphia.

ELECTRO-ANATOMICAL STUDIES ON THE AFFERENT PROJECTION TO THE INFERIOR OLIVE. RAY S. SNIDER and JOHN W. BARNARD, J. Comp. Neurol. **91**:243 (Oct.) 1949.

Snider and Barnard used 10 cats and three Macaca mulatta monkeys for an experimental study of the sites of origin of impulses which reach the inferior olivary nucleus from regions rostral to it. They were especially interested in getting evidence about the time-honored thalamo-olivary tract. Electrical stimuli were applied to various levels of the brain stem through a bipolar electrode of nichrome wire oriented in a Horsley-Clarke stereotaxic machine. The responses resulting from stimulation were picked up in the inferior olivary nucleus by similar bipolar electrodes. These responses were amplified and visualized on a 5-in. (10-cm.) cathode-ray screen and were sometimes recorded by photographing the cathode-ray trace. Histologic sections were made to verify the sites of stimulation. Responses were obtained from a long continuous band, which extended from the diencephalon to the pons. In the cat stimuli applied to the thalamus and basal ganglia failed to produce effects, but in the monkey occasional effects were noted when the head of the caudate nucleus was stimulated. In both cats and monkeys responses were obtained when the lateral hypothalamic area and adjoining structures at the junction of the thalamus and the hypothalamus were stimulated. More caudally, the responsive area moved into the tegmentum mesencephali and the periventricular zone of the midbrain. It finally moved ventrolaterally into the inferior olivary nucleus. Large contralateral responses were noted from the tegmental area of the rostral three-fourths of the midbrain. A cortico-olivary connection is mentioned, but it is not described in detail.

ADDISON, Philadelphia.

THE CALIBER OF CENTRAL AND PERIPHERAL NEURITES OF THE SPINAL GANGLION CELLS AND VARIATIONS IN FIBER SIZE AT DIFFERENT LEVELS OF DORSAL SPINAL ROOTS. BROR REXED and PATRICK SOURANDER, J. Comp. Neurol. **91**:297 (Oct.) 1949.

Rexed and Sourander measured the diameter of the central and peripheral processes of cells in the spinal ganglia of cats. The ventral roots of spinal nerves at selected levels were cut under aseptic conditions, and 14 to 25 days was allowed for degeneration of the severed nerve fibers. At the end of this period the spinal ganglia from the deafferented segments were dissected

out, together with short pieces of their proximal and distal nerves, and serial cross sections were made of these nerves. Fixation was by a mixture of solution of formaldehyde, glacial-acetic acid, and water, and the sections were stained with methyl blue and eosin. In each nerve 400 to 900 myelinated nerve fibers were measured at a magnification of 1,000. The fibers were found to vary from 2 to 16 μ and were tabulated in groups according to their diameter, expressed in microns. The sites of the sections measured were at a distance of about 5 mm. from the poles of the ganglion. A comparison of the results of the measurements of the central and peripheral fibers showed some variation between them but no consistent differences, and the authors accordingly find no indication of a difference in size between the central and the peripheral neurites of the spinal-ganglion cells in the cat.

Rexed and Sourander, with a similar procedure, examined sections of the dorsal roots of cats taken at two locations on each nerve, the first location near the spinal cord and the second near the ganglion. Four pairs of specimens, two from the seventh lumbar segment, 2.5 cm. apart, and two from the first sacral segment, 3.0 cm. apart, were studied. Again, there were variations but no constant differences, and the authors think that the variation between the central and the peripheral levels is not much larger than might be expected from technical causes.

ADDISON, Philadelphia.

A CONTRIBUTION TO THE "CHEMOARCHITECTONICS" OF THE OPTIC TECTUM OF THE BRAIN OF THE PIGEON. ERNST SCHARRER and JOANNE SINDEN, J. Comp. Neurol. **91**:331 (Dec.) 1949.

Scharrer and Sinden studied the sites of enzymatic activities in the optic tectum of the brains of pigeons and compared these sites with the layers seen in Nissl preparations. The methods of Gomori were used for the demonstration of three enzymes—alkaline phosphatase, cholinesterase, and phosphamidase.

Seventeen layers may be recognized by combining the results obtained by methods for cells and for the enzymes. Not all 17 layers are clearly differentiated in the Nissl preparations. Layers 10, 11, and 12 appear homogeneous in the Nissl preparations but may be differentiated on the basis of phosphamidase and alkaline-phosphatase preparations. Layer 13 is visible in cell preparations but does not differ from adjacent layers in enzyme preparations. The authors suggest that biochemical differences may be used as additional criteria for distinguishing layers and areas in the brain.

ADDISON, Philadelphia.

THE PYRAMIDAL TRACT: A STUDY OF SECONDARY DEGENERATION IN IMMATURE NEURONS. A. M. LASSEK, J. Comp. Neurol. **92**:17 (Feb.) 1950.

Lassek has studied particularly the time of degeneration of immature pyramidal fibers in kittens after nearly total extirpation of the cerebral cortex of the left hemisphere. Operations on kittens under 10 days of age were not successful. The mortality was high in older kittens; but 30 animals, which varied in age from 10 to 76 days, survived the surgical procedure, and their brains were examined one to 84 days after operation. Lassek studied pieces of tissue at various points along the pyramidal tract, but the critical observations were made on the pyramids of the medulla oblongata. Two silver stains and two myelin-sheath stains were used in preparing the histologic sections. In general, Ranson's pyridine-silver method was found preferable to the other three.

In kittens up to 3 and 4 months old the pyramidal fibers are all small and uniform in size. After operation degeneration appears in the axons as early as 49 hours and is complete at the end of 5 days. After a similar operation in the mature cat, the largest axons undergo dissolution by the third day after the removal of the cells of origin, whereas the smallest axons react more slowly and may not disappear until 10 days or more. Thus, in the young animals, in which all the axons are of equal diameter, the degeneration is early and affects practically all the axons at the same time, and the whole process is generally completed between the beginning of the third and the end of the fifth day. The myelin sheaths, as judged by the Weigert and osmic-acid methods, were slower to degenerate and disappear than the axons, and some remnants were seen as long as 84 days after operation. The glial response in the kitten is relatively rapid. As seen in the pyramids, it may be well developed during the second and third days.

Whatever may be responsible for the absorption of axons, whether the phagocytic action of the microglia or other factors, the over-all response is initially rapid, and the debris is quickly removed. In the spinal cord sections not much was learned. It was almost impossible to detect signs of degeneration even in the high cervical portions. Lassek suggests that the degenerative phenomena were largely masked by the presence of numerous unaffected fibers, which belonged to other tracts. In human brains up to about one year of age it is normal to find the pyramidal fibers small and of uniform size. Lassek suggests that in the newborn and young human infants, when the pyramidal fibers are sufficiently damaged, the degenerative reaction may be the same as that seen in the kittens; that is, the fibers are more sensitive, and break down and are removed more rapidly than in the adult.

ADDISON, Philadelphia.

AN ATTEMPT TO PRODUCE STRUCTURAL CHANGES IN NERVE CELLS BY INTENSE FUNCTIONAL EXCITATION INDUCED ELECTRICALLY. CHAN-NAO LIU, H. L. BAILEY and WILLIAM F. WINDLE, J. Comp. Neurol. **92**:169 (April) 1950.

Liu and his co-workers sought for evidence of histologic change in the nerve cells of 26 guinea pigs and 11 cats after electrical stimulation of their axons. Both acute and chronic experiments were performed. In the acute experiments the animals were killed on the same day as the stimulation. In the chronic experiments the animals were allowed to live for one to seven days after the stimulation. In all cases pentobarbital sodium was used as the anesthetic Three forms of stimulators were employed. Stimuli were applied for different lengths of time and at different voltages and frequencies. Many precautions were taken to prevent postmortem changes. The animals were perfused with the fixing fluid, and the sections were stained with a buffered solution of thionine at a constant pH of 4.4. Comparison of sections from control and experimental guinea pigs failed to reveal any change of pattern of the Nissl substance. In the cats no changes were seen after stimuli which had intensities below 20 volts. However, with stimuli of 20 volts and more changes were seen in the cats which were allowed to live 60 hours after stimulation. These changes resembled early stages of chromatolysis, and the authors suggest that they may have been due to damage to fibers and subsequent axon reaction in the cytoplasm of the cell bodies.

ADDISON, Philadelphia.

Physiology and Biochemistry

PHYSIOLOGIC CHARACTERISTICS OF REGENERATING MAMMALIAN NERVE AND MUSCLE. J. D. THOMSON, J. A. MORGAN, and H. M. HINES, Am. J. Physiol. **161**:142 (April) 1950.

This investigation was concerned with certain functional characteristics of motor nerve and skeletal muscle during the early stages of reinnervation and regeneration which followed total denervation. Particular attention was given to neuromuscular transmission phenomena and to the response of regenerating skeletal muscle to stimuli applied to newly regenerated motor nerve fibers.

In rat gastrocnemius muscles, early in the course of regeneration of their crushed tibial nerves (21 days after operation), duration of single muscle twitches, particularly the relaxation phase, elicited by nerve stimulation was significantly prolonged. Later in regeneration (35 days) duration of twitches again approached normal values. This prolonged twitch was not due to the presence of a large mass of denervated muscle tissue. The interval between onset of initial shortening and maximal shortening, developed on indirect repetitive stimulation, was significantly less in regenerating than in normal muscle. Since a similar decrease was found in partially denervated muscle, it is not an exclusive characteristic of early regeneration, but may be due to fewer active muscle fibers being reached by nerve impulses, and hence an earlier attainment of summated maximal tension.

There was a greater degree of fusion of individual twitches at low stimulus frequencies (15 and 30 per second) in regenerating than in normal muscle. The extent of wave summation on indirect stimulation was less in regenerating than in normal (control) muscle. A lower stimulus frequency was required to produce maximal summation in regenerating than in normal muscle. A muscle early in regeneration exhibited more rapid transmission fatigue on repetitive indirect stimulation than did a normal muscle. This phenomenon may be due to a deficiency of cholinesterase, although persistent increased sensitivity of muscle to endogenous acetylcholine may also play a part.

ALPERS, Philadelphia.

ELECTROPHYSIOLOGICAL STUDIES OF NERVE AND REFLEX ACTIVITY IN NORMAL MAN: I. IDENTIFICATION OF CERTAIN REFLEXES IN THE ELECTROMYOGRAM AND THE CONDUCTION VELOCITY OF PERIPHERAL NERVE FIBRES. J. W. MAGLADERY, and D. B. MCDOUGAL JR., Bull. Johns Hopkins Hosp. **86**:265 (May) 1950.

The studies reported in this and in the succeeding two communications were undertaken in the course of investigating certain peripheral manifestations of spinal cord reflex activity in man. The first paper describes some of the patterns normally evoked by stimulation of a mixed peripheral nerve in man. For clarity, certain deflections occurring in the action potentials led from innervated muscles, and from the skin overlying the nerves themselves, were designated as M, H, F, and late waves and as nerve action potentials.

Hodes, Larrabee, and German (ARCH. NEUROL. & PSYCHIAT. **60**:340 [Oct.] 1948) remarked on the great contrast between the relatively slow conduction rates detected in certain motor fibers in human limbs and the much higher velocities found in animals and in other motor nerves in man. This discrepancy led the authors to a consideration of "a residual latency," presumably due either to slowed velocity in fine terminal portions of the nerve fibers or to a delay at the neuromuscular junction. This "residual latency" was, however, much greater than myoneural delays found in other mammalian studies. In the present investigation the ulnar nerve trunk was stimulated not only at wrist and elbow, but also at various intermediate sites. Contrary to previous assumptions, it was found that impulses in motor fibers showed a progressive slowing as they proceeded distally throughout the extent of this segment of the nerve trunk. This progressive decrease in conduction velocity over distal segments of a mixed nerve trunk is a feature shared by both motor and afferent fibers. The reason for the slowing is not clear, but it indicates most likely a decrease in fiber size (Gasser, H. S., and Grundfest, H.: *Am. J. Physiol.* **127**:393, 1939), due either to tapering or to branching.

H waves, originally described by P. Hoffmann (Untersuchungen über die Eigenreflexe [Sehnenreflexe] menschlicher Muskeln, Berlin, Julius Springer, 1922), were shown by him to be associated with stretch reflexes. His deduction that they were subserved by afferent fibers of high velocity has been confirmed by the demonstration that conduction rates of these afferent fibers are greater, in the popliteal region, than those of motor fibers in the same segment.

F waves, recorded from different muscles, bear a certain resemblance to the H deflections. They both show a varying temporal relation to the M component when the nerve trunk supplying them is stimulated at different sites. The significance of F reflexes needs much further study.

II. EFFECTS OF PERIPHERAL ISCHEMIA. J. W. MAGLADERY, D. B. MCDOUGALL JR., and J. STOLL, Bull. Johns Hopkins Hosp. **86**:291 (May) 1950.

It was the purpose of this paper to consider the effects of ischemia, as produced by sphygmomanometer-cuff pressure, on certain objective results evoked by low threshold, presumably Grade-A fibers in mixed peripheral nerve trunks in man.

It was found that ischemia, thus produced, has a depressant effect on conduction in group-A motor and afferent fibers in such nerve trunks. This effect is a generalized one throughout the fibers, and not the result of local pressure on the segment directly underlying the occluding cuff.

In representative groups of both afferent and motor fibers, depression occurs earlier and is more profound in proximal than in distal parts of the same nerve fibers. This finding, taken in conjunction with comparative conduction velocities, suggest that a gradient exists for these characteristics throughout the nerve trunks.

In all three instances in which afferent fibers were studied, sensitivity to the effects of ischemia increased with increasing conduction velocity. Motor fibers, however, were somewhat more resistant than certain afferent fibers of slower conduction rate.

III. THE POST-ISCHEMIA STATE. J. W. MAGLADERY, D. B. MCDOUGAL JR., and J. STOLL, Bull. Johns Hopkins Hosp. **86**:313 (May) 1950.

This presentation shows that there are sensory and motor components of the phenomena occurring after restoration of circulation to a previously ischemic limb. The motor components are reflexly induced by the sensory. The site of initiation of the paresthesias has not been identified, but there is good evidence that they arise distally, most probably at sensory endings.

Depression of afferent fibers distal to the occluding cuff has previously been shown to be a general one, but more rapid in onset and more profound in the case of fibers, or those parts of fibers, of highest velocity. Restoration of circulation is followed by recovery, in the same order. Paresthesias make their first appearance at a time when the most rapidly conducting fibers of the nerve recover. This suggests that impulses contributing to the appreciation of paresthesias probably traverse fibers of high conduction velocity and implies that pain pathways are not likely involved.

Possible mechanisms of the initiation of paresthesias are considered. The authors conclude that the results presented in this communication are compatible with an explanation that the phenomena are due to a restitution of normal equilibrium—presumably tonic—which had been disturbed by ischemia. Results of other workers have suggested that the shifts entailed might be those of potassium.

SYNTHESIS OF ACETYLCHOLINE IN CRUSTACEAN NERVE AND NERVE EXTRACT. D. M. EASTON, J. Biol. Chem. **185**:813, 1950.

The acetylcholine-synthesizing system, choline acetylase, has been rather intensively studied in the vertebrate nervous system. Nachmansohn considers the efficiency of the synthesizing system adequate to account for the restoration of acetylcholine that is split during the passage of impulses in the vertebrate nerve. This, he feels, supports his concept that acetylcholine breakdown is a primary phenomenon in the impulse. Gerard has vigorously questioned this conclusion. In view of the small amount of information about invertebrate acetylcholine systems, it seems worth while to report the demonstration of the choline-acetylase system in the nerve tissue of crayfish and crab, thus corroborating the statement of Nachmansohn that this system is present in invertebrate, as well as in vertebrate, nerve tissue. The acetylcholine-synthesizing system has been examined in crustacean nerve tissue, the heart of the clam Venus mercenaria being used as test object. In aerobic incubation of whole isolated nerve cords of the crayfish Cambarus virilis, the total acetylcholine content rose from 22 ± 4 to 49 ± 7 γ per gram of wet tissue during a two-hour period. In anaerobic incubation of acetone powder of nerve tissue of the crab Cancer irroratus, between 45 and 200 γ of acetylcholine per hour per gram of powder was obtained when the saline-extracted powder was incubated in the presence of different activators and adenosinetriphosphate.

PAGE, Cleveland.

EFFECTS OF ACUTE REDUCTION IN BLOOD PRESSURE BY MEANS OF DIFFERENTIAL SPINAL SYMPATHETIC BLOCK ON THE CEREBRAL CIRCULATION OF HYPERTENSIVE PATIENTS. S. S. KETY, B. D. KING, S. M. HORVATH, W. A. JEFFERS, and J. H. HAFKENSCHIEL, J. Clin. Invest. **29**:402 (April) 1950.

Differential spinal-sympathetic-nerve block, achieved by the injection of dilute procaine-hydrochloride solution into the lumbar subarachnoid space, produces a considerable fall in the blood pressure of many hypertensive patients, presumably by blocking the sympathetic outflow to the abdomen and the lower extremities, without loss of skeletal muscle tone. This procedure, therefore, offers a means of studying the response of the cerebral circulation to a drop in blood pressure mediated by dilatation in vascular beds remote from the brain. The use of differential spinal block as a possible screening test in selecting patients for surgical sympathectomy provided an opportunity for undertaking these studies on the cerebral circulation.

Kety and his co-workers report studies on the gases of arterial and internal-jugular-venous blood, cerebral blood flow, oxygen consumption, and vascular resistance in patients with essential hypertension (idiopathic hypertensive vascular disease) before and after a reduction in blood pressure achieved by differential spinal-sympathetic-nerve block.

They found that the high cerebrovascular resistance of essential hypertension is capable of partial relaxation in response to a fall in blood pressure. This relaxation is not complete, with the result that with severe reduction in blood pressure to normotensive levels a significant reduction in cerebral blood flow and evidence of cerebral anoxia occur.

ALPERS, Philadelphia.

CORTICO-CORTICAL CONNECTIONS OF THE WALLS OF THE SUPERIOR TEMPORAL SULCUS IN THE MONKEY (MACACA MULATTA). O. SUGAR, L. V. AMADOR, and B. GRIPONISSIOTIS, J. Neuropath. & Exper. Neurol. **9**:179 (April) 1950.

The greatest area of buried cortex in the temporal lobe lies in the superior temporal sulcus. The corticocortical connections of the cortex buried in the superior temporal sulcus in the monkey (Macaca mulatta) were investigated by the methods of physiological neuronography.

Sugar and his colleagues found that, in addition to strong firing to the adjacent exposed cortex, there are firing pathways to the frontal and occipital lobes. In general, the firing pathways are those which might be anticipated from pathways known from strychninization of the adjacent exposed cortex. From the superior portion (parietal cortex) there is firing into neighboring cortex and, unexpectedly, into the superior part of the premotor area (area 6, *FB*). From the inferior portion of the anterior bank there is firing into the frontal lobe rostral to the arcuate sulcus, the temporo-occipital junction, and the occipital lobe behind the lunate sulcus.

From the posterior bank there is a heavy firing caudally, reaching well into the striate cortex. A fairly well restricted locus in the anterior part of the posterior bank fires heavily into the frontal lobe below the sulcus principalis and in front of the arcuate sulcus. Elsewhere, there is heavy firing into nearby areas of the temporal lobe.

ALPERS, Philadelphia.

INFLUENCE OF INFECTION WITH LANSING STRAIN POLIOMYELITIS VIRUS ON PREGNANT MICE. C. L. BYRD, J. Neuropath. & Exper. Neurol. **9**:202 (April) 1950.

Baker and Baker observed that acute poliomyelitis is more frequent in pregnant women than could be attributed to mere chance or random sampling. The course of the disease in pregnancy does not differ from that in nonpregnant women or in males, but 30.4% of the pregnant women who contract poliomyelitis abort.

Mice are frequently used in experiments with the virus of poliomyelitis, especially for the study of Lansing-type strains. Byrd attempted to ascertain whether mice react similarly to infection with mouse-adapted poliomyelitis virus during pregnancy.

Inoculation with the Lansing poliomyelitis virus was carried out on 227 pregnant mice and an equal number of nonpregnant controls. The disease had a shorter incubation period and caused a high number of abortions in pregnant mice.

ALPERS, Philadelphia.

Neuropathology

HEREDITARY MYOCLONUS EPILEPSY. W. I. MORSE 2ND, Bull. Johns Hopkins Hosp. **84**:116 (Feb.) 1949.

Morse describes the clinical course of two young siblings who had myoclonus epilepsy and subsequently died after episodes of generalized convulsions. Autopsy material was available for study.

From the pathologic point of view, the two youngsters under consideration may be regarded as having had a primary degeneration of the gray matter if one disregards a lesion in the medullary substance of the cerebellum in one child. In this child the destructive process was severer. Morse could not explain the lesions on the basis of hypoxia, and he believes that "we must for the present regard the lesions as effects of a cause that is not yet recognized, this cause acting in different degrees in different cases. This underlying factor, whatever it may be, possibly consists in some hereditary metabolic disturbance of nerve cells, as is thought to occur in amaurotic family idiocy."

In both children there were diffuse central necrotic lesions of the liver, and the pathogenesis is not clear.

GUTTMAN, Wilkes-Barre, Pa.

PSYCHOSES WITH MULTIPLE SCLEROSIS. JOHN K. TORRENS and JOHN L. OTTO, Dis. Nerv. System **10**:243 (Aug.) 1949.

Psychiatric symptoms have long been known to occur in multiple sclerosis, various studies indicating an incidence of 75 to 90%. Euphoria and mild depression are common, but psychotic syndromes are rare, the incidence being perhaps 4%. Pictures of organic deterioration, manic-

depressive reactions, and schizophrenia, characteristically of paranoid coloring, have all been reported, in that order of frequency. Theories in explanation run the gamut from purely organic to purely psychogenic. Signs of psychosis belong chiefly to the acute initial stage or to exacerbations; they appear and disappear quickly, are usually correlated directly with neurologic changes of multiple sclerosis, and are customarily absent in remissions. Longitudinal evaluations of the patients do not reveal the usual developmental patterns of the so-called functional psychoses, a finding in support of the hypothesis that the psychological difficulties are not coincidental but depend on the basic disease. Of 48 patients with multiple sclerosis seen by the authors, two showed concomitant paranoid schizophrenia. In both patients delusions waxed and waned with increase and decrease in activity of the disease, as measured by neurological findings. Both showed mental abnormalities as early symptoms. A concluding warning is given that apparently clear-cut functional psychoses may be primarily multiple sclerosis.

BEATON, Tucson, Ariz.

CEREBRAL CONTUSION IN ACCIDENTAL ELECTROCUTION. G. B. HASSIN, J. Neuropath. & Exper. Neurol. **9**:311 (July) 1950.

Contusion of the brain may be produced by a strong electric current when this is directly applied to the exposed cerebral tissues. Hassin reports an instance in which this occurred in a woman, aged 67, after electrocautery of the fifth nerve.

The histologic changes caused by electric contusion differ from those observable in electric concussion in the prevalence of so-called ball hemorrhages and some parenchymatous changes, such as punched-out holes, disruption of the walls of small blood vessels, and hyaline-like degeneration with ameboid-glia-cell changes. The changes are mainly due to mechanical action of the current, except possibly for the hyaline-like degeneration and ameboid-glia-cell changes, which are evidently the result of excessive heat action.

The histologic differences between the changes of electric concussion and those of electric contusion are due to the mode of application of the electric current, and probably the duration of its action.

Hassin points out that the coagulation method of treatment of trigeminal neuralgia, such as was attempted in this case, should not be used in patients with a vascular disease, such as arteriosclerosis or hypertension.

ALPERS, Philadelphia.

Psychiatry and Psychopathology

PHYSICAL SYMPTOMS MASKING EARLY PSYCHIATRIC DISORDERS. L. G. MOENCH, Dis. Nerv. System **10**:219 (July) 1949.

A great number of patients with psychiatric illness are first seen because of physical symptoms and are given prolonged medical treatment before the mental nature of the disorder becomes apparent. Often the delay entails the loss of the best opportunity for definitive treatment. Too frequently, minor organic defects are accepted as the cause of complaints. Such defects may be incidental and do not prove that the disease is physical. Noting that headache is probably the most universal symptom, the author presents five psychiatric patients, all of whom had headache as an initial complaint. The eventual diagnoses were conversion hysteria, psychopathic personality, schizophrenia, psychoneurotic depression in a setting of constitutional psychopathic inferiority, and involutional melancholia.

BEATON, Tucson, Ariz.

ENCOPRESIS. M. I. PRATT, Harefuah **38**:110 (April 3) 1950.

Encopresis is described as a condition analogous to enuresis—an involuntary passage of feces—and is considered a psychogenic disorder, in contrast to fecal incontinence, which usually has an organic basis. Encopresis is encountered in children of normal intelligence; no cases in girls have as yet been reported. The author considers the condition a conversion phenomenon—a neurotic modality of response to difficult situations, and occasionally to unconscious conflicts. He reports two cases. The first was that of a boy of 10 years with borderline intelligence who on being transferred to a school at some distance from his home, where the studies were some-

what beyond his capacity, manifested encopresis in reaction to his new difficulties by means of regression to the anal level. The second case is that of a boy of 9 years, one of four children, who at the age of 3 years had tuberculosis and was institutionalized for a short time. On returning home, he was unhappy, appeared dejected, and showed sibling jealousy. Enuresis and encopresis developed. He would put fecal matter in various places around the house. The enuresis and encopresis disappeared soon after he was returned to his previous environment.

N. Savitsky, New York.

Meninges and Blood Vessels

Mixed Meningitis: A Case of Combined Pneumococcus and Klebsiella Meningitis with Recovery. J. J. Conn and O. F. Rosenow, Arch. Int. Med. **85**:924 (June) 1950.

The authors report a case of meningitis due to mixed infection with Diplococcus pneumoniae and Klebsiella pneumoniae because a search of the literature failed to reveal such a case.

This case presented several unusual features: absence of nuchal rigidity prior to the first lumbar puncture and its prompt appearance thereafter; clinical signs simulating those of a cerebral vascular accident, and persistence of elevated temperature 33 days after therapy was instituted.

Recovery, with minor sequelae, followed treatment with sulfadiazine, given intravenously, and penicillin and streptomycin, injected intramuscularly and intrathecally.

The primary focus of infection responsible for this mixed meningitis was not determined.

Alpers, Philadelphia.

Ophthalmologic Findings in Spontaneous Thrombosis of the Carotid Arteries. H. S. Sugar, J. E. Webster, and E. S. Gurdjian, Arch. Ophth. **44**:823 (Dec.) 1950.

Although traumatic or surgical occlusion of one or both common carotid arteries or their branches may be asymptomatic, especially in young persons, spontaneous thrombosis of these vessels in a subject with marked vascular sclerosis is more likely to lead to serious neurologic disturbances. In this paper, three cases of optic nerve atrophy, two complete and one incomplete, associated with thrombosis of the carotid arteries are reported.

The optic nerve atrophy in the two cases in which there was unilateral blindness was due to occlusion of the central artery of the retina. In the third case the condition was not associated with any disturbance in the central artery. The two types of involvement of the optic nerve suggest two entirely different causes, the first, secondary to occlusion of the central artery, being the more obvious.

It is well known that ligation of the main arterial trunk which supplies the eye, the internal carotid artery, does not cause blindness, in nonarteriosclerotic persons. The collateral circulation in such eyes is adequate. In persons with arteriosclerosis, the compensatory changes necessary for the development of collateral circulation are insufficient. In addition, it is likely that similar sclerotic changes involve the communicating arteries. Slowing of the blood flow also tends to favor thrombosis. Occlusion of the central artery may result from continuation of the thrombotic process along the main vessel or from sclerotic changes within its own walls, aided by the slowing of the blood flow.

Partial atrophy of the nerve is not due to any changes in the central retinal artery, but is the result of involvement of the nutrient arteries of the optic nerve itself. The sclerotic process affecting these vessels, together with slowing of the blood flow, produces a "spotty" involvement of the optic nerve. This accounts for the irregularity of the visual field in such cases.

Alpers, Philadelphia.

The Anterior Perforating Arterioles and Their Relation to the Internal Capsule. Arthur F. Young and Louis J. Karnosh, Dis. Nerv. System **10**:99 (April) 1949.

Young and Karnosh studied roentgenographically the "striatal arterioles" (lenticulostriate arteries), supplying the general region of the internal capsule, after injection of a special radiopaque material into specific trunks at the base of the brain. They suggest that these

various channels be collectively termed the anterior perforating arterioles. These vessels form a pathologic group in their propensity to aneurysm, carbon-monoxide encephalopathy, thrombosis, and hemorrhage, which is based on a common characteristic of being small vessels emerging from large parent arteries. Striatocapsular branches from the middle cerebral artery consist of short proximal arterioles, which penetrate no deeper than the ansa lenticularis and do not enter the globus pallidus, and longer distal arterioles, which go to the putamen, the internal capsule, and the head of the caudate nucleus. The latter branch richly in the putamen but show no anastomoses in the internal capsule, and there is entire absence of any arteriolar connection from the cortex of the insula. The knee of the internal capsule is reached by short vessels springing directly from the internal carotid artery, while its posterior limb obtains nourishment from the anterior choroidal artery, long and tortuous, arising from the internal carotid artery, winding around the midbrain, and ramifying also into the crus cerebri, globus pallidus, hippocampal gyrus, external geniculate body, and choroid plexus. It is most predisposed to thrombosis, which causes an often misinterpreted syndrome of hemiplegia, hemianesthesia, and hemianopsia. Its only anastomosis is with the posterior choroidal terminations of the posterior cerebral artery, and there is no supracapillary connection in the globus pallidus with the perforating arterioles from the middle cerebral artery. The anterior choroidal arteries are true end arteries. The important anatomicopathological fact demonstrated is the lack of any precapillary anastomosis in the internal capsule, which is supplied only by a capillary pool contributed from the striatocapsular arterioles and the anterior choroid artery. The arterioles found in the internal capsule merely traverse it on their way to the caudate nucleus.

BEATON, Tucson, Ariz.

MENINGEAL REACTION IN RHEUMATIC FEVER. L. NASSI, Rev. clin. pediat. **47**:529, 1949.

Nassi directs attention to the importance of the benign types of meningitis which appear early in the course of the first attack of rheumatic fever. They disappear within three days in the majority of the cases. There are headache, stiff neck, Kernig, Brudzinski and Lasègue sign, and red dermographism. The cerebrospinal-fluid findings suggest serous or lymphocytic meningitis. Relapses occur and may cause blindness or death, or the disease may develop into subacute or chronic meningitis. Treatment consists in spinal punctures and intrathecal administration of small doses of penicillin or streptomycin. Treatment of the first acute attack of rheumatic fever consists of administration of penicillin, sulfanilamide, sodium salicylate, and ascorbic acid. This regimen is continued one month after disappearance of the acute symptoms in order to control the rheumatic manifestations and the residual meningeal inflammation. Fourteen cases of the meningitis in children between the ages of 4 and 10 years are reported.

J. A. M. A.

TUBERCULOUS MENINGITIS AFTER IMMUNIZATION AGAINST TYPHOID. K. AUERSBACH and I. VON BERGMANN, Ztschr. klin. Med. **145**:346, 1950.

Auersbach and von Bergmann say that among 18 patients who were treated at their clinic for tuberculous meningitis there were four in whom the disease developed after immunization against typhoid. Two of the four patients were children, aged 6 and 3 years, and two were girls, aged 18 and 16 years. The meningitis became manifest from 12 days to eight weeks after the typhoid immunization. Three of the four cases terminated in death, and necropsy revealed a caseated primary tuberculous lesion. In three of the patients the existence of tuberculosis was not known when typhoid immunization was performed, but two patients were known to be allergic to tuberculin, and one of these had had pleurisy three months before the immunization. The authors stress that children and adolescents should not be immunized against typhoid unless the result of their tuberculin tests is known. Typhoid immunization must not be performed if the tuberculin reaction is positive or if there are clinical and roentgenologic signs of an active tuberculous process. If such signs are absent, efforts must be made to ascertain the time of primary infection. Immunization against typhoid must be avoided for four years after the primary tuberculous infection.

J. A. M. A.

Diseases of the Brain

INFECTIOUS MONONUCLEOSIS WITH NEUROLOGIC COMPLICATIONS. VERA B. DOLGOPOL and GEORGE S. HUSSON, Arch. Int. Med. **83**:179 (Feb.) 1949.

Dolgopol and Husson report their observations on a patient who was ill with infectious mononucleosis with severe neurologic complications. Until recently, infectious mononucleosis has been regarded as a mild disease, with few complications and with a uniformly favorable outcome. It is certain now that several forms of serious complications are associated with this illness, including hepatitis, thrombocytopenia, myocarditis, spontaneous rupture of the spleen, and involvement of the central and peripheral nervous systems. Multiple serious complications may occur in the same patient.

The patient whose case is described was a 19-yr.-old woman whose symptoms began with malaise, fatigue, backache, and weakness of the legs. In two days there were photophobia, diplopia, and edema of the eyelids. Within five days after the onset of the symptoms, the deep reflexes were noted to be sluggish, and within seven days there was stiffness of the neck. The cerebrospinal fluid was under increased pressure and contained 50 cells per cubic millimeter, with a normal sugar content and no increase in protein. The heterophil-antibody test gave a positive reaction in a dilution of 1:448. On the following day the Kernig and Brudzinski signs were positive; the patient was unable to move her legs and had difficulty in swallowing. The reaction to the heterophil-antibody test was positive in 1:1,792 dilution. Nine days after the onset of the symptoms the patient died.

Examination of the brain revealed severe degenerative changes in the nuclei of the third and fourth cranial nerves and in the inferior reticular nucleus of the medulla. There was degeneration of the Purkinje cells of the cerebellum. In the spinal cord, hemorrhages were present in the gray matter, mainly in the posterior horns, but in the lumbar region the hemorrhages had spread into the anterior horns as well.

Diverse neurologic symptoms in infectious mononucleosis may precede the hematologic changes and the appearance of lymphadenopathy and splenomegaly. Such situations invariably present considerable diagnostic difficulties. The manifestations may be similar to those of meningitis, encephalitis, poliomyelitis, or polyradiculoneuritis. Great aid in the diagnosis of this illness can be derived from a test for the heterophil-antibody, as it has been positive in practically all reported cases of infectious mononucleosis with neurologic manifestations. It would seem advisable, therefore, to perform that test on all patients with obscure or atypical acute neurologic manifestations.

GUTTMAN, Wilkes-Barre, Pa.

BIOCHEMICAL STUDIES IN MULTIPLE SCLEROSIS. H. H. JONES, H. H. JONES JR., and L. D. BUNCH, Ann. Int. Med. **33**:831 (Oct.) 1950.

Fifty patients were studied during the two-year period of this investigation. Blood and urinary-excretion changes were recorded after the oral ingestion of glucose in the 50 patients with multiple sclerosis and in 30 healthy controls. Controls were selected from various occupations, age groups, and morphologic groups to match those of the patients. Urine-excretion studies were started later in the project than the blood studies, so that excretion data were available for only 28 patients and 20 control subjects.

The authors found that in patients with multiple sclerosis there was an abnormal response to oral administration of glucose, the most striking of which was an increase in the pyruvic acid of the blood out of proportion to the lactic acid. In patients in relapse, the fasting level of pyruvic acid was high and remained sc throughout the four hours of the test. In the less active stage of the disease the disproportion of pyruvic acid to lactic acid was not shown until the second, third, and fourth hours after glucose administration. Serum cholesterol was elevated and was higher in patients with active than in patients with quiescent disease. Serum inorganic phosphorus was significantly lower. The excretion of inorganic phosphorus, expressed in ratio with preformed creatinine, was increased over the zero sample in the multiple-sclerosis patients by 72, 24, and 25% during the second, third, and fourth hours after glucose administration, as compared with a decrease of 33, 41, and 36% during the corresponding periods in the controls. The ratio of excretion of uric acid to that of creatinine after ingestion of glucose was lower than normal in the patients in relapse, being little changed from the zero sample in the first and fourth hours.

ALPERS, Philadelphia.

UNILATERAL INTERNUCLEAR OPHTHALMOPLEGIA. D. G. COGAN, C. C. KUBIK, and W. L. SMITH, Arch. Ophth. **44**:783 (Dec.) 1950.

Paralysis of both medial rectus muscles on attempted conjugate lateral gaze without other evidence of third-nerve paralysis is an entity known as internuclear ophthalmoplegia. It is relatively common and almost invariably due to multiple sclerosis. Paralysis of one medial rectus muscle on attempted conjugate lateral gaze is much less common. The purpose of this communication is to report eight cases of unilateral syndrome and to describe the anatomic lesion in one, the latter being the first case of unilateral internuclear ophthalmoplegia in which a pathologic study has been made.

Internuclear ophthalmoplegia is presumed to result from a lesion of the medial longitudinal fasciculus, with consequent interruption of the impulses from a center in the medulla on one side to the medial rectus nucleus on the opposite side. The clinical manifestations consist of paralysis of the medial rectus muscle on attempted conjugate lateral gaze. As a rule there is preservation of convergence. Horizontal, rotary, or vertical nystagmus is frequently present, and it is characteristic for the horizontal nystagmus to be much more pronounced in the abducting eye. A vertical divergence of the eyes (skew deviation) also is often present. The onset is frequently accompanied with vertigo and sometimes with nausea and vomiting.

In every one of the eight cases, the onset was sudden, and there was unilateral paralysis of one medial rectus muscle on attempted lateral conjugate gaze. Convergence was normal in four cases and could not be elicited in four. Nystagmus was present in six cases, and skew deviation, in six cases. In one case, of lupus erythematosus, autopsy was performed, revealing a small region of infarction involving the medial longitudinal fasciculus on the side of the ophthalmoplegia. The pathologic changes in that case and the sudden onset of symptoms and associated vascular disease in most of the other cases were evidence that a vascular lesion was generally responsible for unilateral internuclear ophthalmoplegia.

The authors suggest that, whereas multiple sclerosis is the chief cause of bilateral internuclear ophthalmoplegia, vascular disease (infarction) is the usual cause of unilateral internuclear ophthalmoplegia.

ALPERS, Philadelphia.

ELECTROENCEPHALOGRAPHY IN THE DIAGNOSIS OF HEARING LOSS IN THE VERY YOUNG CHILD. R. E. MARCUS, E. L. GIBBS, and F. A. GIBBS, Dis. Nerv. System **10**:170 (June) 1949.

Education of the hearing-handicapped child, to be effective, must be instituted early, but the diagnosis of profound deafness in the very young is clinically difficult. The authors report an approach utilizing the "arousal response" (waking activity interrupting cortical sleep patterns) in the electroencephalogram of the sleeping child. Various loud, frightening noises were produced, and it was observed that the "arousal response" was obtained when the sound was perceived and was the same as that caused by other types of sensory stimulation. Nineteen patients, from 17 months to 9 years of age, were studied; in 13 no audition could be demonstrated by routine otological testing. Four of the latter group showed some "arousal response." It is concluded that electroencephalography provides a technic for the diagnosis of deafness in the infant and child and that the "arousal response" to appropriate stimuli is an adequate index of hearing. As an additional observation, it was found that of the 13 children with recognized deafness, seven had electroencephalographic abnormality. The remaining six patients, in whom the primary disorder was retarded speech and an associated incomplete reduction in auditory function, all displayed electroencephalographic irregularities. The relation of hearing loss to disorders of the central nervous system should receive further investigation.

BEATON, Tucson, Ariz.

ENCEPHALOPATHY AFTER COMBINED DIPHTHERIA-PERTUSSIS INOCULATION: REPORT OF CASE. I. M. ANDERSON and D. MORRIS, Lancet **1**:537 (March 25) 1950.

Anderson and Morris report on a boy (one of uniovular twins) who had normal health and development until the age of 2 years 4 months, when he was admitted to the hospital because of a generalized convulsion. The duration was short, and he was left with transient right hemiplegia for five hours. He was discharged from the hospital the next day. At the time of this

illness three other children in the same house had mumps, and his illness was diagnosed as mumps encephalitis. At the age of 2 years 7 months, the twins were immunized with combined diphtheria-pertussis antigens. One twin remained well, but the patient had a generalized convulsion 36 hours later. Investigations made eight months later showed dilatation of the left lateral ventricle and diminished electrical activity of the left cerebral hemisphere. A year later there was some recovery, but the patient still had a small vocabulary and was mentally retarded. The pathogenesis is unknown, but, in view of the reports of serious neurologic complications, it is suggested that pertussis vaccination should not be done if there is a history of convulsions in the child or the family.

J. A. M. A.

EARLY DIAGNOSIS OF CEREBRAL PALSY. C. D. S. AGASSIZ, M. B. O'DONNELL and E. COLLIS, Lancet **2**:1030 (Dec. 3) 1949.

Since better results from treatment are obtained when the diagnosis of cerebral palsy is made early, the authors have attempted to establish diagnostic criteria for this condition in children under 6 months of age. Among the muscles affected are those concerned with swallowing, the muscles of the eye and other muscles of the head and neck, and muscles of the upper and lower limbs. Thus, the tongue may be slow-moving or wriggling and irregular in movement; uncontrolled swallowing is difficult, and the baby dribbles from the corner of the mouth. The eye movements are restricted, and there may be a squint. The child may be deaf. He may have difficulty in feeding. One of the helpful signs is the absence of smiling, as even the mentally defective child will usually smile.

The general development of the child with cerebral palsy is retarded, as is manifested in slowness in holding up the head, poor control of the arms and legs, or inability to crane the neck or to avert the head if prone. There may be a persistent grasp reflex, difficulty in abducting the legs and a persistent stretch reflex, so that on flexion of a limb there is resistance to the extension. There is usually retention of the fetal characteristics. At the age of 6 to 12 months the affected child does not attempt to crawl or to climb up in his cot, and the normal flexing of the knees is absent.

Several other tests are described, such as the persistence of the startle reflex and the neck-righting reflex, but these are not reliable. In only 25% of children with cerebral palsy is there mental deficiency. The treatment is more effective when instituted early, but it must be individual, differing for spastic, athetoid, and ataxic types.

MADOW, Philadelphia.

HEREDITY IN HEPATOLENTICULAR DEGENERATION AND INTRINSIC RELATION OF WESTPHAL-STRÜMPELL PSEUDOSCLEROSIS AND WILSON'S DISEASE: NOSOLOGICAL PLACE OF KEHRER'S "ABDOMINAL WILSON'S DISEASE" IN HEPATOLENTICULAR DEGENERATIONS. MICHEL J. ANDRÉ and LUDO VAN BOGAERT, Encéphale **38**:1, 1950.

André and van Bogaert indicate that Wilson did not consider the disease named after him as congenital or abiotrophic, but he did believe that it could be familial. Even as late as 1947, in his "Neurology," he appeared to hesitate in believing that it was hereditary. In 1930, Kehrer arrived at the conclusion that hepatolenticular degeneration was a heredofamilial disease, following a simple recessive mode of transmission. He was convinced that the neural lesions were secondary to those of the liver and that it was primarily on the liver that the hereditary factors bore most heavily. In 1939, Stadler added an important genetic study to the heredity of Wilson's disease. He insisted on the frequent presence of consanguinity of the ancestors of strains with the disease and the symptomatic homotypy of the cases in the same family. He agreed with Kehrer in considering the disease to be due to a simple recessive trait involving the polyglandular metabolism of the liver, the gastrointestinal tract, and, above all, the carbohydrate metabolism of the body.

The article reviews families showing hepatolenticular degeneration reported in the literature, with the pathology noted in these families. In the fourth part of the paper, the authors give full details and genealogic tables for five families with Wilson's disease already studied and previously reported by them, to which they now proceed to add the data of two more family strains never before published. They believe in the nosologic unity of the various forms of Wilson's disease, such as pseudosclerosis, the abdominal form of the disease, and hepatolenticular

degeneration, as well as certain obscure maladies of the liver and gastrointestinal tract coupled with neurologic or mental symptoms, which they consider to be part of this group.

The authors offer the following conclusions: Hepatolenticular disease is familial in 55% of the known strains and appears sporadically in 45%. They agree that it is due to a simple recessive gene. It can sometimes be transmitted directly, without, however, implying any dominance. According to Lisi, in the Insabato family there was direct transmission of Wilson's disease over four generations.

Genetic studies appear to indicate that the majority of pathologic disturbances noted either in the ancestors or in the collaterals were psychiatric (from simple psychasthenia to dementia), neurologic (usually extrapyramidal), or gastrointestinal (stomach, liver, biliary tract). The frequency of gastric carcinoma in certain strains merits attention. The authors' studies of families bear out the conclusions of Kehrer. They affirm the neuropathologic unity of hepatolenticular degeneration in the light of their own data. However, they are not prepared to decide as to the fundamental unity of the various forms. They note that hepatic cirrhosis, at least in any clinical form, is known in the neurologically normal progenitors of any of the subjects of hepatolenticular degeneration. In tainted families Wilsonian cirrhosis without neurologic signs is unusual (less than 10% of cases of hepatolenticular degeneration).

Genetic studies have not proved that pseudosclerosis and pure Wilson's disease coexist in the same family. The abdominal form of Wilson's disease lies on the border between the classic type of hepatolenticular degeneration and pure Wilsonian cirrhosis without specifically detectable neurologic signs. The study of this abdominal type will resolve the problem of the real unity of the hepatolenticular-degenerative group of diseases.

ZINKIN, New York.

ENCEPHALITIS AS A COMPLICATION OF CHRONIC ENDOCARDITIS. FRITZ SOMMER, Wien. klin. Wchnschr. **61**:292 (May 13) 1949.

Sommer reports seven cases of chronic endocarditis of various causes (hemolytic streptococci were identified in three cases and Streptococcus viridans in one case). He points out that in all these cases autopsy showed brain damage, but in only one case were neurologic findings recorded. Pathologic changes in the spinal fluid are emphasized, and ophthalmoscopic examination is strongly advised. Pathologically, the picture is that of metastatic encephalitic foci.

MASON, New York.

PERIODIC PAROXYSMAL PSEUDONEURASTHENIC SYMPTOMS ASSOCIATED WITH POSTENCEPHALITIS. J. AIGINGER and E. NEUMAYER, Wien. klin. Wchnschr. **61**:314 (May 20) 1949.

A review of the clinical symptoms of 50 patients with postencephalitis reveals a periodic recurrence of symptoms similar to those seen in acute encephalitis. Nineteen patients had ocular manifestations; three, sleep disturbances, and five, psychomotor crises with emotional instability; all the patients had signs of vegetative disturbance. The authors are especially impressed with the four-day cycle with which these symptoms—neurologic, psychic, and vegetative, alone or in combination—recur. They postulate that the encephalitic process has damaged the normal day-night rhythm and that a new four-day cycle has been substituted.

MASON, New York.

Diseases of the Spinal Cord

INTRASPINAL MENINGIOMAS SIMULATING DEGENERATIVE DISEASES OF THE SPINAL CORD. A. A. BAILEY and W. McK. CRAIG, Proc. Staff Meet., Mayo Clin. **25**:233 (May 10) 1950.

The authors review briefly some of the commoner syndromes which involve both sensory and motor systems of the spinal cord. The group of degenerative diseases discussed is that which intraspinal tumors oftener simulate: syringomyelia; demyelinating diseases, such as multiple sclerosis; subacute combined sclerosis, and arteriosclerosis of the spinal cord.

Three cases of intradural extramedullary tumors are presented. In all three cases the functions of the pyramidal tracts and posterior white columns were disturbed.

Bailey and Craig point out that, while intraspinal tumors are not common, they must always be considered in the differential diagnosis of syndromes referable to the spinal cord. Examination of the cerebrospinal fluid and visualization of the spinal canal by means of opaque mediums may be of great assistance.

ALPERS, Philadelphia.

PROTRACTED NERVOUS COMPLICATIONS OF TYPHOID FEVER. G. H. JENNINGS, Lancet **2**:1218 (Dec. 31) 1949.

Jennings reports the case of a man aged 31 who had typhoid and manifested signs of neuritis and myelitis approximately seven weeks after onset of the disease. There were atrophy of both legs, weakness in dorsiflexion of both feet, diminution of touch and vibration sense in both feet, great depression of all tendon reflexes in the lower limbs, and tenderness of the calf muscles. Later the patient exhibited signs of pyramidal tract involvement. In the follow-up observation over a five-and-one-half-yr. period, recovery was slow and incomplete.

MADOW, Philadelphia.

ROLE OF CIRCUMSCRIBED ARACHNOIDITIS IN NEUROLOGIC SEQUELAE OF CLOSED INJURIES OF THE SPINE. L. ROUQUÈS and M. DAVID, Rev. neurol. **81**:185 (March) 1949.

Rouquès and David review causes of the development of spinal block some time after a closed injury, namely, cicatrix surrounding a foreign body; hypertrophic changes in bone; scarring following rupture of dentate ligaments; organization of hematoma; epidural inflammation, and arachnoiditis. They note that little importance has been assigned to the last factor.

They report four cases in which either the neurologic state showed continuous worsening after injury (usually involving angulation and compression) or neurologic sequelae developed some time after a spinal injury. In three of the cases there was manometric block. In all a narrow band of iodized-oil arrest was demonstrated in the lumbar region opposite the site of the angulation and injury; the authors therefore stress the importance of study with contrast medium in such cases. Operation revealed a narrow band of arachnoiditis matting the dura and arachnoid, the dissection of which led to material improvement in two cases. The authors point out that stretching of the roots over the angulated vertebrae is not the mechanism responsible for the symptoms; they believe, rather, that the venous stasis caused by the obstruction of the venus plexuses of the cord causes proliferation of connective tissue. The condition should be suspected in any case of delayed onset or progression of neurologic difficulties following injury.

LEGAULT, Washington, D. C.

Muscular System

DERMATOMYOSITIS AND SCLERODERMA: UNUSUAL CAUSES OF DYSPHAGIA. R. B. LEWY, Arch. Otolaryng. **51**:31 (July) 1950.

Among the unusual causes of dysphagia are scleroderma and dermatomyositis.

In dermatomyositis, in addition to the dermatitis, frequently acute, and myositis, there is generalized angiitis. Pain is usually a prominent symptom. Muscles are weak and tender, and all muscles are atrophied, particularly those of the upper arm and shoulder girdle. Erythema or edema of the skin is often present. Pigmentary and atrophic changes occur later. Increased creatine in the urine is characteristic and should be looked for.

In scleroderma, acute dermatitis is usually absent. Creatine in the urine is not increased. The formation of considerably more collagen is the rule, and there is more evidence of low-grade infiltration of the lower layers of the skin and less of necrosis of the musculature.

ALPERS, Philadelphia.

DIABETES MELLITUS IN ASSOCIATION WITH MYASTHENIA GRAVIS. A. M. PERRY, J. A. M. A. **143**:1332 (Aug. 12) 1950.

Perry reports a case of diabetes mellitus in association with myasthenia gravis. The patient had the typical symptoms of myasthenia gravis: ptosis, diplopia, ophthalmoplegia, and, finally, the appearance of dysphagia and weakness of the extremities. The manifestations were most pronounced after sustained effort and disappeared after rest. The course was characterized by exacerbations and remissions.

Injection of neostigmine methylsulfate, 0.5 mg. intravenously, resulted in a dramatic increase in the strength of the patient within one-half hour and almost complete disappearance of the ptosis. The diabetes was well controlled on a mixture of 30 units of crystalline zinc insulin

and 10 units of protamine-zinc insulin. This regulation failed to abolish or improve any of the signs or symptoms of myasthenia gravis. Subsequently, the oral administration of 90 mg. of neostigmine bromide, in six divided doses, daily resulted in almost complete disappearance of muscular weakness, ptosis, and ophthalmoplegia.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

INTRATEMPORAL SARCOMA OF THE FACIAL NERVE. K. KETTEL, Arch. Otolaryng. **52**:778 (Nov.) 1950.

Tumors arising from the facial nerve are rare, and in all cases previously described the histologic picture has been that of a neurinoma. A case of malignant intratemporal tumor of the facial nerve has not been recorded. Kettel reports such a case.

Peripheral, almost complete, facial paralysis had developed during a 14-month period in a woman aged 57. Except for the paralysis, nothing abnormal was found on otologic, neurologic, or roentgenologic examination. A diagnosis of Bell's palsy was erroneously made, and decompression of the facial nerve was performed 14 months after the onset. An irregular, solid tumor, the size of a small hazelnut, was found, arising from the descending part of the facial nerve, having destroyed the osseous wall of the Fallopian canal and expanded into the deeper mastoid cells. The tumor, a neurogenous spindle-cell sarcoma, was resected and a nerve graft inserted.

Kettel points out that in a case of Bell's palsy with no sign of spontaneous recovery after two months of observation a decompression should be performed, primarily, because this operation has proved its value in cases in which the condition rightly must be classified as Bell's palsy, and, secondarily, because one may be dealing with an intratemporal tumor of the facial nerve.

ALPERS, Philadelphia.

CLINICOPATHOLOGIC INVESTIGATION OF EIGHT CASES OF FATAL POLYGANGLIONEURITIS. L. LARUELLE and M. REUMONT, Rev. neurol. **81**:169 (March) 1949.

Laruelle and Reumont give the name *"polyganglio-névrite"* to a disease characterized clinically by rapid onset of generalized motor and sensory polyneuritis, involving spinal and cranial nerves simultaneously (not progressively or in an ascending fashion), without prodrome other than lassitude and fatigue and without fever and other general symptoms. The spinal fluid is usually normal, with albuminocytologic dissociation in two cases. Paresthesias, rather than pain or aching, predominate; there is weakness without frank paralysis. The distribution does not tend to be distal or radicular; asymmetry is frequent, and there are no meningeal signs.

The disease has a specific pathologic picture, previously reported in isolated cases by various investigators and easily distinguished from other diseases, such as herpes or rabies. The earliest, most characteristic, and most intense lesions are in the spinal- and cranial-nerve ganglia, where widespread, intense hyperplasia of the satellite corpuscles of Cajal takes place. These small cells surround the sensory-cell bodies in the spinal- and cranial-nerve ganglia and are analogous to the cells of the sheath of Schwann. Edema accompanies this, but the lesions are otherwise purely proliferative and hyperplastic, and there are none of the usual evidences of inflammatory reaction, such as perivascular or meningeal lymphocytic response, and no vascular engorgement. Huge collars of small, flat, endothelium-like cells surround ganglion-cell bodies in something of an onion-skin arrangement.

Similar proliferative changes take place about the ventral-horn cells of the spinal cord and the motor cells of the cranial-nerve nuclei. There is also striking proliferation of the adventitia of precapillary arterioles and capillaries, without engorgement. All the changes described can be found in patients dying as early as the fourth day. Extensive changes may be seen in the vagal ganglia before any change in the nerve itself.

Subsequent changes take place in the nerve cell, which is strangled by the proliferation. Peripheral nerves and, less intensely, their roots show degeneration of myelin with hyperplasia of Schwann cells, degeneration of axis-cylinders, and intense hyperplasia of interstitial connective tissue. There is generalized stimulation of the glia in the cerebral gray matter with formation of glial nodules.

The authors believe that the disorder is a distinct entity in the group of polyneuritides.

LEGAULT, Washington, D. C.

Treatment, Neurosurgery

CLINICAL USE OF E. C. 110, A NEW HEADACHE REMEDY. L. G. MOENCH, Dis. Nerv. System **10**:143 (May) 1949.

Moench states that ergotamine with caffeine (cafergot®), a combination of 1 mg. of ergotamine tartrate and 100 mg. of caffeine, has been an effective compound for oral use in the treatment of those headaches, such as migraine, which are due to abnormal blood vessel pulsation. Of 21 patients with cephalalgia due, variously, to tension, encephalitis residuals, and migraine, 17 have had satisfactory relief and one equivocal relief. Three patients, all psychoneurotic, were not helped. No serious side effects have been observed, though nausea and vomiting, abdominal cramps, restlessness, tremor, and insomnia have occurred. The optimum dose seems to be one or two tablets, taken at the first warning of a headache.

BEATON, Tucson, Ariz.

PHENURONE IN EPILEPSY. MARK ZEIFERT, Dis. Nerv. System **10**:245 (Aug.) 1949.

Zeifert reports on 13 cases of refractory grand mal and psychomotor epilepsy treated with phenacemide (phenurone®) in doses of 1.5 to 2.5 gm. daily. Only a few patients could be maintained seizure-free on phenacemide alone; most required other anticonvulsants. However, patients whose attacks could not be checked on other combinations were brought under control when the new drug was added. When it was withdrawn, spells again became frequent. Though no statistics are offered, it was observed that the most dramatic effect of phenacemide was in cases of psychomotor epilepsy. No way was learned of determining which patients with this variant of the disease would respond, and some subjects with personality disorders were made so much worse that the therapy had to be stopped. On the other hand, two men who were notoriously untractable have become cooperative and pleasant. Side effects have included dysesthesias, palpitation, insomnia, drowsiness, rash, weakness, headache, and anorexia. Euphoria and exaggeration of character instability were noted in five patients; regression to an infantile level was present in three. In at least one, toxic reactions did not appear during a second course of therapy, indicating that tolerance may be developed. No special blood effects were found, though the white blood cell count tended to drop about 10% in the first seven to 14 days of treatment. Blood-sugar levels decreased 10% to 15%, and 50% of patients showed depression of serum albumin. The cephalin-flocculation test showed a trace to a 1+ reaction in three patients shortly after treatment was begun, but none of the patients had laboratory proof of true hepatic damage. There is evidence that persons taking phenacemide do not conjugate hippuric acid, for after treatment with the drug was started hippuric acid excretion declined sharply, and crystals having a different microscopic appearance and melting point appeared in the urine. It is stressed that further studies are needed before dismissing the danger of hepatic injury.

BEATON, Tucson, Ariz.

USE OF SECONAL SODIUM IN ELECTROCONVULSIVE THERAPY. W. M. GYSIN and R. G. WITHAM, Dis. Nerv. System **10**:315 (Oct.) 1949.

In treating a large group of patients with electric shock, the use of curare has been found impractical because time-consuming, owing to the necessity of slow administration of the drug and a relatively long interval of waiting for its optimum effect. As substitute premedication, the authors have found secobarbital sodium exceedingly satisfactory, administered intravenously in doses adjusted for weight, body habitus, and heaviness of musculature. The crystalline compound is dissolved in a strength of 1 grain (0.065 gm.) to the cubic centimeter, and 3 to 4 cc. is given in five to eight seconds. Shock is administered 40 seconds later. Though some well-developed patients require up to 90 seconds for full relaxation, as a rule the convulsive threshold is measurably increased after 40 seconds. There seems to be no contraindication to the slight augmentation in voltage and time necessitated by the drug. Of 103 patients treated by this method, 9 (8.7%) had postshock fractures, only one of them having a major break. There is no important difference in the strength of the initial tonus when secobarbital and when curare

are used. Apprehension before therapy was almost universally abolished by the barbiturate, and there was no memory of the application of electrodes and mouth gag. Agitation was only rarely a problem; most patients were free of sedative effect one to two hours afterward, and memory defects appeared infrequently. No serious respiratory embarrassment was observed, in contrast to the poor color sometimes seen in persons given curare. Secobarbital is definitely superior for cardiac patients, and even those with decompensation or auricular fibrillation tolerate it without aggravation. It is concluded that secobarbital provides a greater margin of safety than curare or the other barbiturates.

BEATON, Tucson, Ariz.

FATAL APLASTIC ANEMIA FOLLOWING TRIDIONE ADMINISTRATION. S. R. KAPLAN, G. LEVY, and S. O. SCHWARTZ, Dis. Nerv. System **10**:339 (Nov.) 1949.

The majority of reports on trimethadione (tridione®) emphasize good clinical results, with few toxic side effects; but the literature contains six accounts of deaths from aplastic anemia, and several studies have stressed the danger of neutropenia. In 1947, Davis and Lennox found that 13.3% of a series of 137 patients had a white blood cell count of 2,500 or less. The authors describe the case of a woman aged 21 who for a year had been taking trimethadione (12 grains [0.78 gm.] three times a day) for the control of grand mal epilepsy. On entrance to the hospital her red blood cell count was 2,350,000; her hemoglobin, 6.8 gm. per 100 cc., and her white blood cell count, 2,450, with 2% neutrophils, 1% monocytes, and 97% lymphocytes. The platelets numbered 31,000 per cubic millimeter, and the bleeding time was over 15 minutes. No marrow could be aspirated from sternum or iliac crest. In spite of therapy with numerous transfusions, penicillin, toluidine blue, rutin, and folic acid, she died on the 28th day after admission. Consent for autopsy was denied. The necessity for constant surveillance of the blood picture during use of trimethadione is insisted on; the drug should be permanently discontinued at the first sign of depressed myeloid function. Once clinical manifestations of pancytopenia appear, the chances of recovery are slim. The early recognition of the complication and immediate discontinuation of the compound make marrow recovery possible, but subsequent administration may have consequences equally or more serious. It is suggested that the effect of trimethadione on the marrow is an actual toxic destruction, rather than action through a hypersensitivity factor.

BEATON, Tucson, Ariz.

SOME POINTS IN MANAGEMENT OF INFANTILE CEREBRAL PALSY. J. H. CROSLAND, Proc. Roy. Soc. Med. **41**:406 (June) 1948.

A picture of the total disability, including the motor deficit, sensory deficit (deafness, etc.), and degree of associated intellectual and psychologic deficit is necessary to the adequate management of the child with cerebral palsy. For the very young and for the child with poor home environment, the residential treatment center is probably best. But because the child leads a normal home and community life and the mother is instructed in his management, the day center has distinct advantages, especially as the teaching of the mother provides for the necessary long-continued treatment program.

In general, the earlier the treatment begins the better, although it may be difficult to determine accurately the child's mental ability at the age of 1 year. At this early period the development of bad movement patterns in the child's effort to overcome his disability may be obviated. The child should sit in a chair as soon as possible, and crawling is not frowned upon, but he should not be allowed to stand or attempt to walk until his program is well advanced. Respiration and proper feeding are important. The use of a simple tune is helpful in his keeping an interest in his exercises. He should not be overworked, or his powers of concentration overtaxed by the enthusiasm of his parents and teachers. Rest periods are essential. The spastic type of patient is often extremely fearful, and a feeling of security must be maintained; often the spastic child needs more urging than the athetoid child. The keynote of management of the athetoid child is relaxation. When relaxation is attained, he must be taught purposeful movements under his volitional control.

BERRY, Philadelphia.

CASE OF MARKED S-CURVE SCOLIOSIS AND MARKED LORDOSIS TREATED BY ELECTRIC SHOCK THERAPY AND CURARE. S. KWALWASSER, Psychiatric Quart. **24**:17, 1950.

Kwalwasser describes the case of a woman, aged 48, who had been suffering from a severe agitated depression for eight months. She had kyphoscoliosis and lordosis. Her mental condition was becoming progressively worse. She had to be spoon- or tube-fed, required attention for her bowel and bladder functions, and was becoming generally feeble and malnourished. She showed an immediate response to electric shock and curare therapy. She was quiet, polite, alert, and cheerful after her fourth treatment. She took care of all her own needs and wants. She seemed to have insight into the fact that she had been mentally ill. Therapy was discontinued after the ninth treatment. Recovery appeared established. Severe skeletal deformities do not preclude electric shock therapy in combination with curare.

J. A. M. A.

PROPHYLAXIS OF HEADACHE FOLLOWING SPINAL ANESTHESIA. JUAN PABLO CACCIA, Prensa méd. argent. **35**:2511 (Dec. 31) 1948.

Caccia noted an incidence of headaches of 18% following spinal anesthesia. The headaches usually appeared 24 to 72 hours after the anesthetic was administered and persisted two or three days. The author was able to reduce the incidence of such postanesthetic cephalalgia to 4% by adding to the anesthetic 100 mg. thiamine hydrochloride in an isotonic sodium chloride solution. Headaches which appeared in these patients were less severe and did not last as long.

N. SAVITSKY, New York.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

James L. Poppen, M.D., Presiding
Regular Meeting May 17, 1951

Physiological Changes Following Frontal Lobe Surgery for Chronic Mental Illness.
DR. ALBERT F. AX and DR. MILTON GREENBLATT.

Seven physiological indices (pulse rate, stroke volume, respiration, face temperature, hand temperature, hand sweating, and muscle tension) have been simultaneously recorded on 26 psychotic patients just before and four months after lobotomy. Stimulation periods consisted of rest, three interviews, and tests with three physical stimuli. Two aspects of the variables were scored: (1) the resting level and (2) the reactivity to stimuli.

The following findings were highly significant:

1. A negative correlation of —0.65 for face temperature and the object-sorting test. This means that the higher the face temperature, the poorer the performance in object sorting. Since other evidence suggests that high face temperature is related to anxiety, it is suspected that the anxiety is the common factor responsible for this correlation.

2. A positive correlation of high physiological reactivity and both tension and disintegration, which were rated by a clinical psychiatrist. This may indicate that in some psychotic persons marked physiological reactivity may lead to tension, and in others it may promote disintegration.

3. A regular postoperative decrease in pulse rate, face temperature, and sweating. This may be taken to indicate a decrease in sympathetic tone (associated with decreased anxiety).

4. Reduction in the inspiration-respiration ratio, apparently also a sign of decreased anxiety.

These changes were shown not to be a function of repeated tests, because no such changes occurred in replication.

The more drastic bilateral operation was followed by greater reactivity of pulse rate and face temperature, but by a lower reactivity of hand temperature, than was the less drastic unilateral and bimedial operation.

Our data suggest the hypothesis that psychotic patients whose physiological characteristics resemble an epinephrine-like state are more likely to recover than those whose characteristics resemble a non-epinephrine-like state.

DISCUSSION

DR. MAX RINKEL: Dysfunctions of the autonomic nervous system present themselves in a variety of simultaneous manifestations, many of which are often merely expressed subjectively. With the "polygraph," it is possible to objectivate autonomic manifestations and record a number of them simultaneously, thus permitting their correlation. Carrying out Dr. Greenblatt's idea of many years, Dr. Ax, by connecting electric receiving devices with channels of the electroencephalograph, converted the Grass machine into a polygraph. With this method, our knowledge of the physiology of the autonomic nervous system has been greatly advanced. The authors are to be highly commended for the excellent paper they presented.

DR. SAMUEL BOJAR: Were the patients, on whom Dr. Funkenstein's tests were used, examined before and after lobotomy?

DR. HARRY C. SOLOMON: These studies will add to our knowledge of what happens when there has been some major disturbance in the situation that existed in the course of the psychosis and was modified by a change produced by the surgeon.

DR. JAN STEVENS: Were the patients kept in the hospital three or four months after operation? What change is found in untreated patients in the wards of the state hospitals? What is the change in autonomic response after a general surgical operation?

DR. MILTON GREENBLATT: The question concerning differentiation of fear and anger on a physiological level should be answered by Dr. Ax.

It has taken Dr. Ax three years to get ready to present this paper—a year and a half to develop this remarkable apparatus. When he first came to the Boston Psychopathic Hospital, those of us who had been looking to the electroencephalograph for answers to emotional problems were in a stage of increasing disappointment. While we believed that emotion was, at least in part, in the head, the cortical indicators were disillusioning. The only other place to turn was to the periphery. Dr. Ax followed that idea and brought into the picture this remarkable polygraph, which made it possible to record from the periphery. He stuck to the original idea of having a large number of indicators going at once so that he could get this panorama. Through his efforts, several variables may be combined and reduced to indices. At first, many experienced workers thought there would be too many problems and too great a body of data for analysis, but Dr. Ax has come through on most of these questions.

When Dr. Ax spoke of replication before and after lobotomy, it was usually within a short period—two weeks, but rarely more. Two control series would be vital. One of them would be replication of experiments on control psychotic subjects after four months of hospitalization, but without operation. We have data on such a control group, but they are not yet analyzed. We have no data on the state four months after operations on the brain other than lobotomy, but we should be interested in getting them.

Dr. Albert F. Ax: The tests Dr. Funkenstein made on these patients, I believe, have not yet been analyzed in terms of the outcome, but this will be done. We are not quite ready to say anything definite about fear and anger. In a study we made last summer on 16 normotensive patients in whom we stimulated fear and anger, we found two different patterns. They were interpreted as the anger and fear state, the latter being characterized by an autonomic response similar to that produced by injections of epinephrine. The anger response was not purely that of nor-epinephrine, but the patterns were shifted in that direction. We are repeating that study with more subjects, employing the stimulation of fear and anger. We are testing some of the same subjects with injections of epinephrine and nor-epinephrine to see whether the difference between fear and anger lies in that direction. We have not yet demonstrated the pattern differences beyond doubt.

Dr. James L. Poppen: Will the polygraph be better than the lie detectors now used?

Dr. Albert F. Ax: It might be, but I doubt it.

Dr. Max Rinkel: J. E. Hoover wrote me that the F.B.I. does not believe that any polygraphs, or lie detectors, are reliable, and the F.B.I. rejects them completely.

Observations on Dynamic Changes After Prefrontal Lobotomy. Dr. Elizabeth Zetzel.

This paper is based essentially on a pilot study, rather than definitive research. Problems of dynamic research in the field of organic cerebral pathology are extremely complex. It is essential to distinguish between results attributable to defect and results which represent dynamic reactions to disease or injury. Clinically, this distinction leads to differentiation of quantitative and qualitative results. In cases so far seen, almost all long-term results appear attributable to quantitative changes—in particular, diminution of anxiety and tension. This leads to flattening of affect, typical of lobotomized patients. In addition, however, interesting and stimulating dynamic changes have been observed in a small number of patients, particularly in the early months after operation. These changes appear to represent dynamic defensive reactions to cerebral damage comparable to those observed in other organic diseases, for example, dementia paralytica. Further research in this field may lead to interesting information with regard not only to the dynamics of organic disease, but also to the psychopathology of psychotic illness.

DISCUSSION

Dr. Wilfred Bloomberg: I am interested in the juxtaposition of these two papers—the physiological and the psychoanalytical approach. Today, at the Veterans Administration Hospital in Framingham, we discussed two patients with a condition diagnosed as pemphigus, one of whom was relieved of symptoms by corticotropin, and the other by eight months of psychotherapy.

Dr. Ives Hendrick: Many psychoanalysts have shown intense interest in the possibilities of studying deep psychological changes produced by lobotomy and other organic therapies. Unhappily, though, with the exception of Jan Frank and Heath, none have found time to

implement this interest by thorough research. Dr. Zetzel's efforts promise, therefore, to become a pioneering contribution of great significance. There is a possibility of a clue in such studies to the complete scientific mystery of the unquestioned relation of specific mental content to cerebral physiology. I think Dr. Zetzel's observations are astute and the preliminary organization of her material excellent. But I do not agree that studies are essential for the understanding of schizophrenia.

DR. WEINBERGER: The question of psychological improvement following severe organic disease sometimes arises in the medical service of a state hospital. A woman with severe deteriorated schizophrenia became clear during an acute illness, but went back to the schizophrenic state after recovery. This raises the question of damage to the body, as well as to the brain.

DR. JAY HOFFMAN: I share the impression of Dr. Zetzel, which is also that of Dr. Jan Frank, that these patients are incapable of free association and that it is not possible to develop a transference with them. Any attempt at a dynamic interpretation of their communications is extremely difficult and generally frustrating. It is a striking feature of most lobotomized patients I have seen that they generally deny that any surgical procedure has taken place. The question arises as to whether such denial is the direct result of the surgically produced damage to the brain structure or whether it is a psychological reaction to the brain damage. Another question that I should raise is suggested by one of my lobotomized patients, who showed practically no clinical improvement over a period of two years after the operation. Then, dramatically, striking improvement was apparent. Did not such a delayed reaction suggest that the clinical improvement was not the direct result of the surgically produced damage to the brain but, rather, was a psychologic reaction, slow in appearing, to the cerebral damage itself?

DR. MILTON GREENBLATT: The general dissatisfaction with surgery as a method of treatment of mental diseases needs little elaboration. It is fair to take advantage of surgery for mental disease in investigation, but one should not rest content with the old method of lobotomy, for methods involving far less damage are apparently proving themselves as adequate as the older method. This is true of our bimedial operation, with which there are fewer untoward reactions. Dr. K. Livingston has described an operation in which he creates a pocket between the anterior cingulate gyrus and the rest of the brain. He claims that this operation, which produces less damage than the bimedial one, is as effective as the others.

DR. ELIZABETH ZETZEL: In respect to Dr. Hendrick's comment concerning the significance of the operation, I have a certain amount of material which I did not give for want of time. I have, however, nothing about the immediate postoperative period. In England, I had in analysis for a short period a patient in whom lobotomy had not had any permanent results. After a very short period of improvement, she relapsed to substantially her preoperative state. Her reaction to the operation was extremely negative and masochistic. At the Boston Psychopathic Hospital I have seen at least one patient who has shown considerable anger concerning the operation. I have seen another patient who tends to react to lobotomy in the way depressive patients often do toward shock therapy, by demanding treatment. This patient was given a unilateral lobotomy and has since been asking clamorously for the "other half." As Dr. Hoffman says, with a great many deteriorated schizophrenic patients it is difficult to get information on this subject. They either deny they have had an operation or tend to deny any personal significance. If any meaning is attached, it is of a minor kind, relative to some delusional system, rather than to any real sense of something important having happened. I agree that the distinction between quantitative and qualitative factors is difficult, but I think it is helpful. In interviewing patients and in trying to build up in my mind some picture of the patient before and after operation, I have found a difference between those patients whose anxiety at key points has led to shifting of symptoms. The reactions, which I feel to be direct defensive reactions to the damage itself, resemble the temporary improvement one often sees in schizophrenic patients in severe physical illness. I still think these temporary dynamic changes offer a field for research in schizophrenia, as well as in organic conditions. Anything which makes for qualitative alteration in the patient—fragmentation of symptoms after illness or operation—gives an avenue of approach to the dynamics of the illness. I feel it is something that is worth investigation, particularly as many of these reactions appear to be temporary. In discussing this question with Dr. Frank, I find that he, too, is interested in this aspect of the problem and that there is research going on with the aim of finding some way of producing temporary lobotomy without bringing about the permanent changes so hampering to the patient.

News and Comment

FELLOWSHIP IN MEDICINE

Applications are being received for a two-year fellowship in medicine at New York Hospital-Cornell Medical Center to work with Drs. Harold G. Wolff, William H. Dunn, and Stewart Wolf. One-half time is spent in experimental work, and one-half time in clinical experience with patients with stress disorders. The term begins in July, 1952.

VETERANS ADMINISTRATION RESIDENCIES IN NEUROLOGY

There are available several residencies in neurology under the Veterans Administration Program and the United States Public Health Training Program at Bellevue Hospital. For information, please write Dr. S. Bernard Wortis, Professor of Psychiatry and Neurology, New York University College-Bellevue Psychiatric Division of New York University College of Medicine, 477 First Ave., New York 16.

STANDARD NOMENCLATURE OF DISEASES AND OPERATIONS

Fourth Edition

The American Medical Association announces the publication of the Fourth Edition of "Standard Nomenclature of Diseases and Operations." Changes in the new edition have been as much as possible kept to a minimum. Nevertheless, advancing knowledge has made necessary a complete revision of the section on the psychobiologic unit, diseases of the hemic and lymphatic systems, and tumor etiology. A completely new feature of this edition is the inclusion of code numbers of the International Statistical Classification of Diseases, Injuries, and Causes of Death, parenthetically in the body of the book, and a cross reference of International and Standard code numbers as an appendix. The new edition is being published for the Association by The Blakiston Company (Philadelphia) and will be available Jan. 2, 1952.

Obituaries

GEORGE BORIS HASSIN, M.D.
1873-1951

George Boris Hassin was born in southern Russia, at Zinovievsk (Elizavetgrad), on Aug. 19, 1873, and died of a massive intracerebral hemorrhage in Chicago on Aug. 15, 1951. His father was a melamed, a teacher in a private Hebrew school (cheder). There were five sons and five daughters in the family. His father lacked but a few days of living a century, so that Dr. Hassin did not think that he would die at the youthful age of 77.

He was educated in the gymnasium of Kherson, from which he graduated in 1892. He entered the University of Kazan for the study of medicine and graduated in 1897. It is interesting that in Russia of that epoch, in which there were severe restrictions for Jews (the University of Kazan admitted only 3%), nine of the ten children obtained a professional education (six physicians, one pharmacist, one midwife, one dentist). One of his brothers studied with Kocher when Harvey Cushing was there. The youngest son became a structural steel worker and died in Detroit.

In medical school he supported himself by tutoring and caring for a retired army officer who had an advanced case of tabes dorsalis. Hassin thought dementia paralytica was developing also because he talked always of his brother who was ambassador to Siam. In later years Hassin met, in San Francisco, a Russian, Dr. Stelrod, who had been the personal physician of this brother, who had really occupied the post of ambassador to that country. The symptoms of this patient intrigued the young physician and turned him towards neurology. Bechterew had left Kazan for Petrograd, but Hassin had Darkschewitsch for a teacher. Among his other teachers was a very brutal professor of physiology, a Jugoslav named Horwath, who used to open the abdominal cavity of rabbits before the class to show the peristaltic movement of the intestine to the students. This gave Hassin an aversion to physiology which he never overcame. He prepared his thesis with the professor of pathology, Wisotsky, who was interested in experimental cancer. Hassin took cancers obtained from the operating room, ground them, and injected the emulsions into dogs. Later the serum from these animals was injected into similar cancers in patients. The injections were very painful, and this work also helped to give him an unconquerable aversion to experimental investigation. But, for these studies, he was given a gold medal, which was presented to him at a grand ceremony, for which he bought a secondhand Prince Albert coat.

While in medical school he had heard of the need for physicians in Siberia. So he pawned his medal for 100 rubles and set out, arriving finally in Yeniseisk, 500 miles north of the Arctic Circle, where he would have frozen had not a judge to whom he had a letter of introduction lent him the money to buy a fur coat to replace his Prince Albert.

Hassin remained in Yeniseisk for three years. This was a favorite place of exile for political prisoners, especially Polish, among whom was an ancestor of Dr. Bronislav Onuf (rowitz), who was born there. He subscribed to the *Semaine*

médicale, in which he read of operations for appendicitis, intubations for laryngeal edema, hysterectomy for adherent placenta, and many other treatments for which he had neither facilities nor training. These were conditions he had been obliged to treat with opium and mustard plasters. He became very dissatisfied with his practice and prepared to go to Paris, when the Siberian army was mobilized to go to Peking to suppress the Boxers. The Chinese surrendered before the Russians arrived. As soon as he was demobilized, Hassin went to Paris, where he arrived in December,

GEORGE BORIS HASSIN, M.D.
1873-1951

1900. He was not very happy there and left for Vienna in July, 1901. There he met a pale, hungry, half-starved student named Marburg, who took him to Obersteiner's laboratory. In order to impress me with Marburg's appearance at that time, he used to show me an illustration in Mark Twain's "Roughing It" (American Publishing Company, Hartford, Conn., 1884, p. 433). At that time in Vienna were such well-known physicians as Howard Ricketts, L. Pierce Clark, and Irving Spear. They attended the clinics of Wagner-von Jauregg, Elzholz, Krafft-Ebing, Nothnagel,

Neusser, and Schrötter. Hassin also frequented Benedikt's clinic. He even called on Sigmund Freud, who was a friend of his teacher, Darkschewitsch, with whom Freud had studied in Charcot's clinic. He tried to organize a group of students to attend a course of lectures by Freud but could induce no one to join him. During this time there came to Vienna a Dr. Robertson, proprietor of the Livermore Sanitarium in San Francisco. Obersteiner told Robertson that Hassin had thought of going to San Francisco, inspired by a prospectus he had found somewhere about the new Leland Stanford University. Robertson gave him a hearty invitation to settle in that city. So Hassin visited Berlin for a few weeks and then took a ship to New York, where he landed May 9, 1902, and went by train to San Francisco. Dr. Robertson was astounded to see him and put him to examining urines in the sanitarium. After eight weeks, as he sat on a bench in the park, looking out over the Pacific Ocean towards Siberia, which he lacked the money to reach, he decided that this would not do. He had read that there were many Russian miners in Leadville, Col. When he arrived and found snow all around him, he felt as though he were back in Siberia. This was after the great period of Leadville. The bottom had dropped out of silver prices in 1893. The Matchless Mine, which once had poured out $80,000 a month, was closed. H. A. W. Tabor, owner of the Matchless, had died in 1899. His wife, Baby Doe, was living in a shack near the shaft of the mine with their daughter, Silver Dollar. But there was still much activity in the neighborhood. The principal surgeon in Leadville was Sol Kahn. Hassin called on him; he was very cordial but did little to help. While there, Hassin wrote an article for Kahn on motor and sensory paralysis, which was published in the *Medical Record* of New York. For this Kahn paid him $50. Hassin was much interested in the charlatans who set up tents and, with beating of drums and the wriggling of dancing girls, tried to attract patients for treatment. He called on one named Sullivan, who chewed tobacco and kept spitting over Hassin's head into a cuspidor. This was too much for the former Siberian. These men surpassed even the Siberian shamans. So Hassin moved to Denver, paid $30 for a month's board and room in a Jewish boardinghouse and, by the end of the month, had made exactly $1 in practice.

In Denver he met a Dr. Spivack, an excellent gastroenterologist, who had settled in Denver because he had tuberculosis. This Dr. Spivack lent him $50 on his gold medal. With this money he came to Chicago, intending to continue on to New York and then return to Russia as soon as he could find the means.

Hassin arrived in Chicago on Sept. 1, 1902, and stayed all night in a flophouse for 50 cents. Here he made his first acquaintance with bedbugs. He had a letter to a Dr. Sahud, whose brain he examined years later and described (*J. Neuropath. & Exper. Neurol.* **8:** 757-784, 1948) and who introduced him to a pharmacist. He rented a room at 14th Street and Newberry Avenue and saw patients in the back of the pharmacy. The first patient referred to him by the pharmacist was a woman who wanted an abortion. Hassin told her he did not know how to do it. The second patient was a woman who was bleeding after an abortion. Hassin told her he did not know how to stop it. But slowly he developed a practice, passed the state board examination, which someone had told him about, and acquired an office on Racine Avenue with an old physician named Poliataroff. This doctor lived largely on sardines and crackers, which he bought by the case and shared with Hassin. The latter also developed a taste for sardines and ultimately died with a

tin, which he had just opened, in his hands. In this building lived the mother of Dr. Isadore Diamond, later his friend and collaborator. When the mother told her son of the doctor whose room was full of books, Diamond called on him. At that time Diamond, who had been trained in pathology with Flexner, was working at Rush Medical College with Hektoen. Hassin went with Diamond to call on Hektoen; he wanted to work on the pathogenesis of tabes. But Hektoen was not interested, and nothing came of his visit, except that he there made the acquaintance of Bassoe.

Having much time on his hands, he began to write articles for an obscure medical journal in Chicago called the *Clinical Review*—first one on the pathogenesis of tabes and then one on the clinics of Nothnagel, which he elaborated from the notes he had taken in Vienna. At the time of the Russo-Japanese War he wrote also an article about medicine in Siberia for *The Journal of the American Medical Association*. Through this article he became acquainted with Dr. Lee Mettler, professor of neurology at the old College of Physicians and Surgeons. Dr. Mettler was writing a textbook, which the students were supposed to buy, but had no clinic and no dispensary. He got Hassin to correct the manuscript and read the proofs. Then he asked him to start a dispensary; Hassin persuaded Diamond to help him. Diamond protested that he knew no neurology, but Hassin had his way with him, as usual. Together they opened a dispensary and clinic in 1909 in a basement room, which they carried on until 1914. Diamond was useful to Hassin in a number of ways; he had a good general pathological training, which Hassin lacked, and he excelled at psychotherapy, which Hassin never understood.

Hassin took the examination for attending neurologist to the Cook County Hospital in 1911, but the examination was voided because it was proved that the surgeons had previous knowledge of the questions. He took the examination again in 1913 and passed, but went to Germany to study in April, 1914. In Hamburg Professor Nonne told Bostroem to give the *Amerikaner* a few lumbar punctures to do. Hassin overheard the remark, was outraged by it, and never returned to the Clinic. Instead, he went to Jakob's laboratory and started working on neuropathology. Josephy was in the laboratory at that time. When the war broke out, there was much speculation as to how long it would take Germany to win. When Hassin suggested that perhaps Germany might not win, there were loud guffaws of laughter. Hassin told me once that the one who laughed loudest was Josephy, who lived to see Germany lose two wars and himself an expatriate. On leaving the laboratory, Hassin asked Jakob how much he owed for instruction. Jakob suggested that he might pay when Germany lost. During the inflation which followed the war Jakob's microscope was stolen, and Hassin presented him with a new one.

The war obliged Hassin to return to Chicago. He now opened an office on State Street as a specialist in neurology but continued to care for many families, which he had treated as a general practitioner, as long as he lived. At this time Clarence Neymann was superintendent of the Cook County Psychopathic Hospital. He gave Hassin a small laboratory and lent him a microscope. Here Hassin began to work on his old problem—the pathology of tabes—but soon entered the United States Army and was assigned to the Army Research Laboratory under Lewis Weed. C. Judson Herrick and James B. Ayer were also working in this laboratory at that time. In 1918 another examination was held at the Cook County Hospital,

and Hassin, Meyers, Pollock, and Krumholz became attending neurologists. In 1920 Meyers resigned and went to California. At the suggestion of Bassoe, Hassin had John Favill appointed to the vacant place. The service was then Hassin and Favill until 1941.

It was at the beginning of this period that I made the acquaintance of Dr. Hassin. I was studying abnormal psychology at the University of Chicago. The instructor took us to the Psychopathic Hospital, where Dr. Bayard Holmes was trying to cure dementia praecox by irrigating the colon through appendiceal fistulae. This subject did not interest me much, so I wandered away and came upon a little man in a coat, like Joseph's, of many colors from the stains he was using, who invited me to look at what he was examining under the microscope. I admitted that I did not know what it was. "What are you studying?" he asked. "Abnormal psychology," I replied. "Don't be a sap," he said, "study something you can see," and began a long discourse about ameboid glia, clasmatocytes, and other esoteric things, terminating with the invitation to collect a small group to which he could give a series of talks about neuropathology. I do not remember all the members of the group, but Marion Hines and George W. Bartelmez were among them.

In April, 1919, I went to the clinic of Harvey Cushing in Boston. But in December I was notified that I had passed the County examination and should report on Jan. 1, to begin my internship. Having third choice of services, I knew that I could trade them so as to remain on neurology. Dr. Cushing was annoyed at my leaving, and also intrigued to know what sort of a man it might be for whom I would desert his clinic. It turned out as I had supposed in the County Hospital, and I remained happily on Dr. Hassin's service for six months. Then somebody reported me to the warden, Dr. Karl Meyer. I expected he would discharge me, but he listened attentively to my explanation of the reasons for my strange actions and then offered me the residency at the Psychopathic Hospital. I accepted and continued to work with Dr. Hassin in the laboratory. This laboratory was very primitive. We had only an old freezing microtome and had to clean and use old discarded slides and cover slips from the general laboratory, but Dr. Hassin's enthusiasm made up for all deficiencies. I continued there until October, 1920, when I returned to Boston.

In 1920 Dr. Hassin resumed teaching at the University of Illinois and was appointed histologist to the State Psychopathic Institute by its director, Dr. H. Douglas Singer. He now moved his laboratory to the Research and Educational Hospitals, followed by the faithful Diamond. At first he had great difficulty in getting his studies published. Patrick was editor of the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. One day he came to Bassoe and complained indignantly of an upstart who had dared to present a manuscript with a bibliography in a dozen different languages. "Obviously a bluffer," said Patrick, and rejected the article in spite of Bassoe's mild caution. Bassoe solved the difficulty in his usual diplomatic way by giving Hassin brains to examine and signing the studies of them with Hassin so that Patrick had to accept them. When Singer became the chief editor, there was no more difficulty in finding a place to publish. About the same time (1922), Harvey Cushing became president of the American Neurological Association. One day he told me that he was going to propose me for membership and asked, "What about that staining friend of yours in Chicago?" I approved warmly,

and so it came about that Dr. Hassin and I were elected in the same year. He had now a national forum, of which he made good use, and became notorious for his fiery rejoinders to those who had the temerity to question his opinions.

His course now was steadily followed until 1941. With his service at the County Hospital, his dispensary at the University of Illinois, and his scientific work, he was fully occupied but found time to write the best textbook of neuropathology in any language. His reputation steadily grew during this period. He was busy, respected, and healthy, and probably gave little thought to the possibility that this period must some day end. He was seriously disturbed when he had to retire at the age of 68 from his professorship and service at the County Hospital. He was childless, and his wife had died. In casting about for some way to occupy his time, he bethought himself of his early difficulties in getting his work published and decided to found a journal to be devoted to neuropathology. Dr. Oldberg gave him facilities in the Illinois Neuropsychiatric Institute and permitted him to continue his neuropathological and editorial work. Only with great difficulty did I persuade him to include experimental neurology in his journal. It was then that I learned the sources of his deep emotional aversion to experimental medicine. With this journal he was busy and happy for many years. It took the place of his wife, his children, and his pupils; it was his very life. When it was rudely and unnecessarily taken from him, he never recovered from the hurt. In a spasm of outraged desperation he started another journal, which he gave a name as nearly like that of the previous one as possible. I tried to dissuade him but, finding him adamant, agreed to be the associate editor. This journal he decided to publish himself and mobilized his few relatives, his patients and their families, and put them all to work. Nevertheless, the burden was heavy and the annoyances many. It was more than he could carry.

This picturesque figure in the neurological world will be missed sorely. He was an indefatigable and systematic student. He read voluminously and made careful notes of all he read. In his study were found numerous packages of notes, dating even from his student days in Russia, all neatly wrapped and labeled. His knowledge of the literature of neuropathology was encyclopedic. I remember the last meeting of the Chicago Neurological Society which Patrick attended. Patrick announced that he intended to talk about the great neurologists he had known and then disappear from the Society forever. In the course of his remarks, he referred to an article on tabes which he had published in the *Illinois Medical Journal* in 1901. When he had finished, Hassin arose and said that he had enjoyed the talk but wished to correct an error; the article of Dr. Patrick was published in the *New York Medical Journal* in 1903. Perhaps I have not remembered the data correctly, but at the time I checked; Hassin was correct, and this was the man Patrick had called a bluffer.

During the long years when he was alone he worked steadily and persistently. Then, in 1924, he married a handsome Norwegian girl—Margaret Hammond. He was very much in love with her; once he expressed his astonishment to Dr. Oldberg that a man could be so literally lovesick. But, evidently, his lifelong habits were difficult to change, since I found the following in one of his notebooks: "4/20/51. The laboratory life was so engrossing that there was not much time to think of something else. My late wife would occasionally ask me, 'And why did you go

marry?' I could give her only one reply—'Ask me something easier.' And so years went after years, decades after decades, until finally I was reminded that I am an old man." Yet they seem to have been fairly happy together. When their twin sons died shortly after birth and she became ill with malignant hypertension, he took her to Hawaii, to Norway, and about Europe. After her death he cared for the aunt who had reared her, during an equally long and painful illness.

Dr. Hassin never forgot his humble origins. The poor and downtrodden always had his sympathy, and often his aid, but they rarely imposed on him without paying for it. He was enthusiastic about the Russian revolution and, in spite of many disappointments, never lost his faith that the Russian people would finally achieve a liberal democratic government. I remember, when I was working in his laboratory, he complained of the time he had to waste climbing stairs to collect his rents. "Why do you not put the task in the hands of an agent?" I asked. "No," he replied, "an agent would squeeze them. I do not want they should be squeezed." He was always very indignant when he was called into consultation and the physician suggested that he charge an amount which he considered excessive. After he founded his journal, he would spend endless time trying to improve an article sent to him by some rather obscure author and labor to put the article into what he considered good form so that he could publish it. "He has worked so hard over it," he would say, "we must make it worth publishing." Of course, these alterations did not always please the author, but he meant well.

He was, in his own way, very generous. He contributed to many causes, often anonymously. He spent a great deal of money on the care of a niece who had a chronic ailment. When he entertained, he did it lavishly, in Russian style. Of course, he did not throw his money about. When one knows his life, that was not to be expected, but when he thought something worth doing, he did not spare expense, if he could not induce someone else to do it. Many of his other traits were caused or accentuated by his past experiences, for example his belligerency. Most of his life he had to struggle for a place in the scientific world. What wonder that he defended that place sometimes with seemingly needless vehemence! His short stature also probably aided in making him stand on his dignity, and memories of the attitude of the society in which he grew up, where professors had exalted social standing. I shall never forget his outraged outburst when an ebullient resident affectionately laid a hand on his shoulder.

In later years he grew more opinionated. It was impossible to discuss anything with him. One could only agree with him or avoid him. When aroused, he was a master of invective. The only person I ever knew to shout him down was an Irish Catholic bishop. I think he was very conscious of his lack of general biological culture and fearful of being led onto an unfamiliar terrain. So long as he remained on the sure ground of observed fact, his histological descriptions were scrupulously accurate, but when he ventured to draw physiological conclusions from them, as in the case of hydrocephalus, for example, he was apt to go astray.

He was the most brutally frank person I have ever known. No one ever had any doubt about where he stood in Dr. Hassin's esteem. He gave no quarter and asked none. He stood always essentially alone and wanted no allies. He was always ready to fight for his opinions and for what he believed to be his rights. His ardor and tenacity made him a redoubtable opponent. He took little part in

Jewish affairs and observed none of their holidays or regulations. But he never tried to make people forget that he was Jewish. The matter seemed to have no interest for him; he neither flaunted his Jewishness nor apologized for it.

Physically he was a small man, of stocky build, with Tatar blood evident in his brachycephalic head and prominent epicanthic folds. I remember going with him to the World's Fair on Long Island. We visited the Turkish pavilion; the guard persisted in talking to him in that language and would not believe that he was not a Turk. Perhaps this was in part responsible for the sadistic pleasure he seemed to find in insulting and browbeating his assistants and associates, especially Diamond, who, I must admit, seemed to enjoy it as much as he. His belligerent frankness cost him many friends. He broke with Favill after Favill was divorced and never spoke to him again. Perhaps his most intimate friend in his later years was Dr. George Halperin. He loved to listen to Halperin read Pushkin. He lived alone in the large apartment which he had furnished for his wife. In it he had spent the happiest years of his life, and he could not bring himself to leave it.

I admired him for his sincere love of scholarship, for his tenacious pursuit of learning, for his honesty and frankness, for his love of the underprivileged, for the kind heart under the belligerent exterior. My life has been richer for having known him; some of the color and spice of life left with him.

PERCIVAL BAILEY, M.D.

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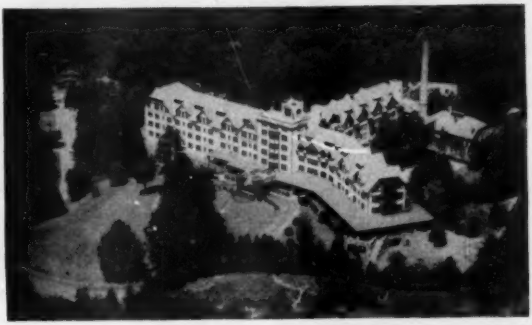

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